EXPRESSION OF ANDROGEN RECEPTOR IN PRIMARY BREAST CANCER

Dissertation submitted in

partial fulfilment of the requirements for the degree of

M.D. (PATHOLOGY)

BRANCH - III

GOSCHEN INSTITUTE OF PATHOLOGY AND ELECTRON MICROSCOPY

MADRAS MEDICAL COLLEGE

CHENNAI – 600 003

THE TAMIL NADU

DR. M.G.R. MEDICAL UNIVERSITY

CHENNAI

APRIL 2016

CERTIFICATE

This is to certify that this Dissertation entitled **"EXPRESSION OF ANDROGEN RECEPTOR IN PRIMARY BREAST CANCER"** is the bonafide original work of **Dr.SOFIYA.C,** in partial fulfillment of the requirement for M.D., (Branch III) in Pathology examination of the Tamilnadu Dr.M.G.R Medical University to be held in April 2016.

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DECLARATION

I **Dr.SOFIYA.C,** solemnly declare that the dissertation titled **"EXPRESSION OF ANDROGEN RECEPTOR IN PRIMARY BREAST CANCER"** is the bonafide work done by me at Institute of Pathology, Madras Medical College under the expert guidance and supervision of **Prof. Dr. M. SARASWATHI, M.D.,** Professor and Director of Institute of Pathology, Madras Medical College. The dissertation is submitted to the Tamilnadu Dr.M.G.R Medical University towards partial fulfillment of requirement for the award of M.D., Degree (Branch III) in Pathology.

Place : Chennai

Date : **Dr. SOFIYA.C**

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INSTITUTE ETHICS COMMITTEE
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CERTIFICATE OF APPROVAL

To

Dr.C.Sofiya
Post Graduate M.D.(Pathology)
Madras Medical College, Chennai -3.

Dear Dr. C.Sofiya

The Institutional Ethics Committee has considered your request and approved your study titled "Expression of androgen receptors in primary breast cancer" No.06102014.

The following members of Ethics Committee were present in the meeting held on 7.10.2014 conducted at Madras Medical College, Chennai -3.

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2. Dr.V.Vimala,M.D. Dean,MMC,Chennai-3	: Deputy Chairperson
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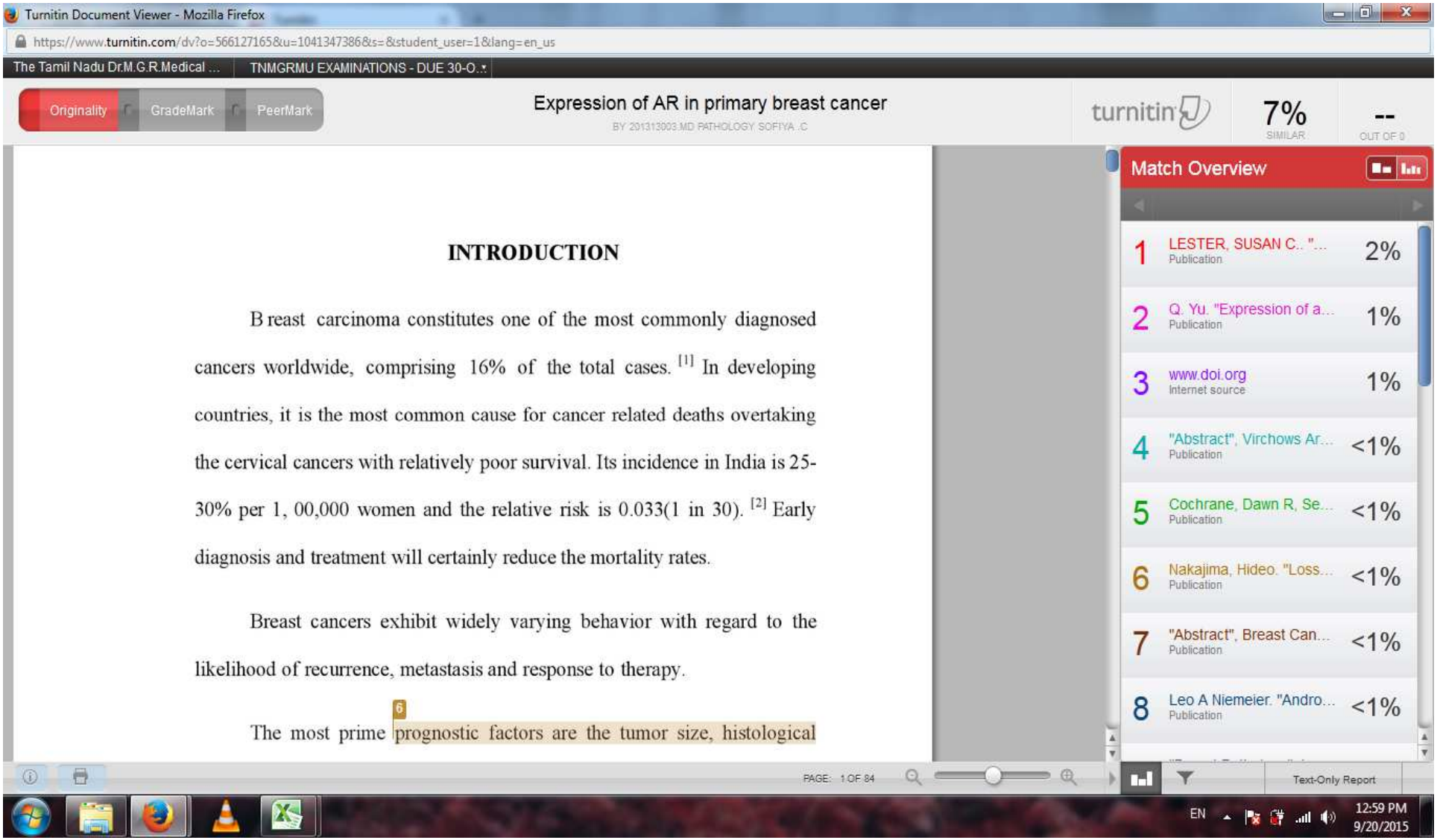
11.Tmt.Arnold Sauline,M.A.MSW	: Social Scientist

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

9/10/14

Member Secretary, Ethics Committee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INTRODUCTION
B reast carcinoma constitutes one of the most commonly diagnosed cancers worldwide, comprising 16% of the total cases. [1] In developing countries, it is the most common cause for cancer related deaths overtaking the cervical cancers with relatively poor survival. Its incidence in India is 25-30% per 1, 00,000 women and the relative risk is 0.033(1 in 30). [2] Early diagnosis and treatment will certainly reduce the mortality rates.
Breast cancers exhibit widely varying behavior with regard to the likelihood of recurrence, metastasis and response to therapy.
The most prime prognostic factors are the tumor size, histological
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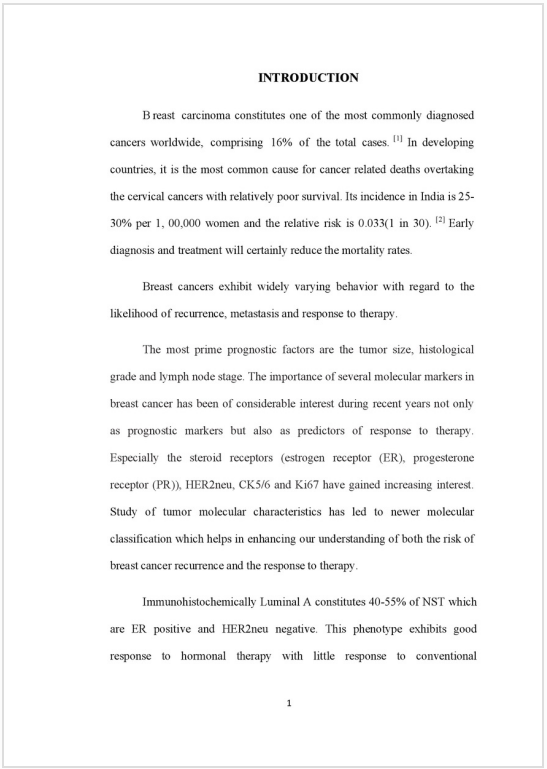

INTRODUCTION

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Breast cancers exhibit widely varying behavior with regard to the likelihood of recurrence, metastasis and response to therapy.

The most prime prognostic factors are the tumor size, histological grade and lymph node stage. The importance of several molecular markers in breast cancer has been of considerable interest during recent years not only as prognostic markers but also as predictors of response to therapy. Especially the steroid receptors (estrogen receptor (ER), progesterone receptor (PR)), HER2neu, CK5/6 and Ki67 have gained increasing interest. Study of tumor molecular characteristics has led to newer molecular classification which helps in enhancing our understanding of both the risk of breast cancer recurrence and the response to therapy.

Immunohistochemically Luminal A constitutes 40-55% of NST which are ER positive and HER2neu negative. This phenotype exhibits good response to hormonal therapy with little response to conventional

1

ABBREVIATIONS

ER	: Estrogen receptor
PR	: Progesterone receptor
AR	:Androgen Receptor.
RNA	: Ribonucleic acid
DNA	: Deoxy ribonucleic acid
HER2	: Human epidermal growth factor receptor 2
CK 5/6	: Cytokeratin 5/6
ICMR	: Indian council of medical research
EGFR	: Epidermal growth factor receptor.
GCDFP	: Gross cystic disease fluid protein.
DCIS	: Ductal carcinoma in situ.
P53	: Protein 53
RT PCR	: Reverse transcriptase polymerase chain Reaction
FISH	: Fluorescent in situ hybridisation
BRCA	: Breast cancer antigen
LHRH	: Luteinizing hormone releasing hormone

CONTENTS

EXPRESSION OF ANDROGEN RECEPTOR IN PRIMARY BREAST CANCER

ABSTRACT

INTRODUCTION: Breast carcinoma has become the most common malignancy in the female population and is one of the leading causes of mortality among women in India. The most important prognostic factors are the tumor size, histological grade and lymphnode stage. The importance of several molecular markers in breast cancer has been of considerable interest during recent years not only as prognostic markers but also as predictors of response to therapy. Especially, the steroid receptors (estrogen receptor (ER), progesterone receptor (PR)), Her2neu, CK5/6 and Ki67 have gained increasing interest. The androgen receptor (AR) is one such newly emerging biomarker. However the clinical significance of its expression in breast cancer patient remains unknown.

AIMS AND OBJECTIVS: To assess the expression of androgen receptors in primary breast carcinomas and to compare the clinicopathological parameters, ER, PR and HER2neu expression with AR expression in breast carcinoma.

MATERIALS AND METHODS: 212 cases were studied for ER, PR and HER2neu expression. From them 50 cases were randomly selected and subjected to Immunohistochemical detection of Androgen receptor. The difference among variables was calculated by Chi square test.

RESULTS: Of the total 212 cases studied, 51.42% cases were positive for ER, 46.7% cases were positive for PR and 26.89% cases positive for HER2neu. Luminal A subtype constitutes 12% cases. AR is expressed in 60% cases. AR expression was significant in ER and PR positive cases and luminal B subtype. However AR is expressed in 31.25% of triple negative cases.

CONCLUSION : AR is expressed in significant number of breast cancers and expression parallels ER and PR expression. It could be an independent prognostic marker and additional AR related targeted therapies can be done.

KEY WORDS : Primary breast carcinoma, Androgen receptor, ER, PR, HER2neu

INTRODUCTION

Breast carcinoma constitutes one of the most commonly diagnosed cancers worldwide, comprising 16% of the total cases. [1] In developing countries, it is the most common cause for cancer related deaths overtaking the cervical cancers with relatively poor survival. Its incidence in India is 25-30% per 1, 00,000 women and the relative risk is 0.033(1 in 30). [2] Early diagnosis and treatment will certainly reduce the mortality rates.

Breast cancers exhibit widely varying behavior with regard to the likelihood of recurrence, metastasis and response to therapy.

The most prime prognostic factors are the tumor size, histological grade and lymph node stage. The importance of several molecular markers in breast cancer has been of considerable interest during recent years not only as prognostic markers but also as predictors of response to therapy. Especially the steroid receptors (estrogen receptor (ER), progesterone receptor (PR)), HER2neu, CK5/6 and Ki67 have gained increasing interest. Study of tumor molecular characteristics has led to newer molecular classification which helps in enhancing our understanding of both the risk of breast cancer recurrence and the response to therapy.

Immunohistochemically Luminal A constitutes 40-55% of NST which are ER positive and HER2neu negative. This phenotype exhibits good response to hormonal therapy with little response to conventional

chemotherapy in a minority of cases and includes well and moderately differentiated carcinoma and is seen in post-menopausal women.

Luminal B constitutes 15-20% of NST which expresses ER & HER2neu receptors. This phenotype responds well to chemotherapy and indicates higher grade and higher proliferative index. It is associated with frequent lymph node metastasis.

13-25% of NST are basal like which expresses neither ER/PR nor HER2neu.

The androgen receptor (AR) which is a marker seen in prostate emerges as a newer biological marker in breast cancer. However it's significance of expression and its implication in patients with breast tumor remains undetected.

Several studies show that there is significant expression of AR in breast tumor cases and proved it as a marker of prognostic significance. Many drugs which target AR are under study in breast cancer.

In this study of 60 cases which included invasive ductal carcinoma no special type (IDC NOS) and its special variants, an attempt has been made to evaluate the expression of Androgen receptor by immunohistochemistry. Further the histological grade, expression of hormonal receptors like ER, PR and other prognostic factors were correlated.

AIMS AND OBJECTIVES

1. To identify the relative frequency and distribution of breast carcinoma in the population.

2. To study the histomorphological features of breast carcinoma including grade, lymph node status, lymphovascular invasion, lymphocytic response and necrosis.

3. To assess the expression of ER, PR, HER2neu in invasive breast carcinomas.

4. To assess the expression of Androgen receptor in these cases.

5. To compare the clinic-pathological parameters and Androgen receptor expression in breast carcinoma.

6. To assess the correlation between the expression of Estrogen, Progesterone Receptors and Androgen Receptor.

REVIEW OF LITERATURE

Carcinoma breast is the most commonly detected solid epithelial tumor in women and it is one of the cancers commonly described in ancient literature due to its visibility. [3] It represents diverse group of tumors that vary in clinical behavior and response to treatment.

Invasive breast carcinomas are malignant duct epithelial tumors which exhibit invasion into adjacent tissues and has increased risk of distant metastasis. [4]

The oldest description of breast cancer was given in 1600 BC by Edwin Smith Papyrus and first case was documented in 2650 BC by Imhotep. [5]

In 1874, the nipple changes that accompany breast cancer was studied and described by Paget and it continued to bear his name. [6] Radical mastectomy was first performed by William Stewart Halsted in 1882. X-rays were discovered by Wilhelm Conrad Roentgen in 1895 and it forms the basis for mammogram and radiotherapy.

In 1925, the first grading system for breast cancer was evaluated by Greenhough. [7] Grading breast cancer with tubule formation, nuclear pleomorphism and hyperchromasia was proposed by Scarff et al in 1928. Later in 1957 WHO adapted the numerical scoring system based on tubule formation, nuclear pleomorphism and Mitosis [8] which was proposed by Bloom and Richardson. In 1990, Nottingham modified the Bloom and Richardson's grading system. [9]

EPIDEMIOLOGY

As per National Cancer Registry Programme ICMR (2009-2011), breast cancer is the most common cancer in most cities of India which constitute 25%-30% of all female cancer and is second most common in rural areas. [10]

In India, the crude incidence rate of breast carcinoma is 85/100,000 women / year. [11] The death per incident ratio is highest in India, with 50%, compared to 30% in China and 18% in the US.

It is more common in age group of 50-60 years constituting 69% of breast cancer. India is rapidly stepping towards industrialization resulting in lifestyle changes. This probably contributes to the increase in breast cancer incidence in our country.

The annual age-adjusted rate is 30-33 per 1, 00,000 in urban women and 8.6 per 1, 00,000 in rural women. [12]

Histology and molecular analysis showed breast carcinoma is a heterogeneous disease composed of morphologically and genetically distinct entities with different molecular profile, behavior and response.

RISK FACTORS

A variety of risk factors are identified based on Epidemiological studies combined into BCRAT (Breast Cancer Risk Assessment Tool). [13, 14]

1. **AGE-** Peak age group is at 75-80 years in older studies. But current studies show a drastic shift in the age group towards younger age group. [10]

2. **HORMONES-** The function of Estrogen in Breast is stimulation of cell growth and proliferation. It acts as a transcriptional activator by activating via Estrogen Receptor. [15] As per Women's health initiative trial in 2002, there is reduction in incidence of ER positive mammary carcinoma with decrease in Hormone replacement therapy. [16]

3. **GENETICS-** About 12% of breast cancers is thought to be hereditary Mutation in BRCA1 and BRCA2 account for majority of the cancers. [17, 18]

BRCA 1 gene is present in chromosome 17q. The product of the gene is responsible for DNA repair. Apart from breast cancer, this mutation also has increased risk of ovarian cancer and pancreatic cancer. [19, 20]

BRCA 2 gene is located in chromosome 13q and this mutation is associated with high risk of male breast carcinoma, cancers of Pancreas, Prostate and Cutaneous Melanoma. [21, 22] BRCA 2 gene associated breast cancers are poorly differentiated but more often ER positive than BRCA1 associated cancers. [23]

Genomicide association studies (GWAS) found out a number of genes associated with cancer risk including FGFR2, PTEN, CDH1, TP53 gene. [18]

Le Fraumeni syndrome (familial cancer syndrome) is associated with P53 tumor suppressor gene mutation. Ataxia telangiectasia patients with Cowden syndrome are also associated with increased risk of breast cancer.

4. **SPORADIC BREAST CANCER**- Risk factors like Gender, Age at Menarche, Menopause, Reproductive history, Breast feeding are based on duration of Hormone exposure. Recently, a non-genomic pathway which act via G-protein coupled receptor GPR 30 and does not involve ER is identified. These result in activation of Metalloproteinase which then act on EGFR and results in cell proliferation. [24] Hence drugs targeted on ER may not be enough to inhibit all cancers.

5. **ENVIRONMENTAL FACTORS**

a) Diet: High dietary fat is one of the significant predisposing factors for breast cancer.
b) Alcohol increases the risk of breast cancer.
c) Radiation: Women treated with mantle radiation for Hodgkins lymphoma have 20% to 30% risk of breast carcinoma development.

6. **OTHER FACTORS**

a) Carcinoma of the contralateral breast (or) endometrium – have increased risk of breast cancer.
b) Breast carcinoma has peculiar association with meningioma. [25]

CARCINOGENESIS AND TUMOR PROGRESSION

Early lesions like Atypical Ductal Hyperplasia, Atypical lobular hyperplasia show increased expression of Hormone receptors and abnormal regulation of Proliferation. [26, 27] Loss of heterozygosity is seen in carcinoma in situ lesions.

Majority of Carcinomas arise from ER expressing luminal cells. Some ER negative tumors arise from myoepithelial cells which are explained by the finding that many myoepithelial proteins are shared by triple negative or basal like carcinomas. [28, 29]

Another theory explains that these tumors can arise due to loss of ER expression from previously ER positive precursors. [26, 30]

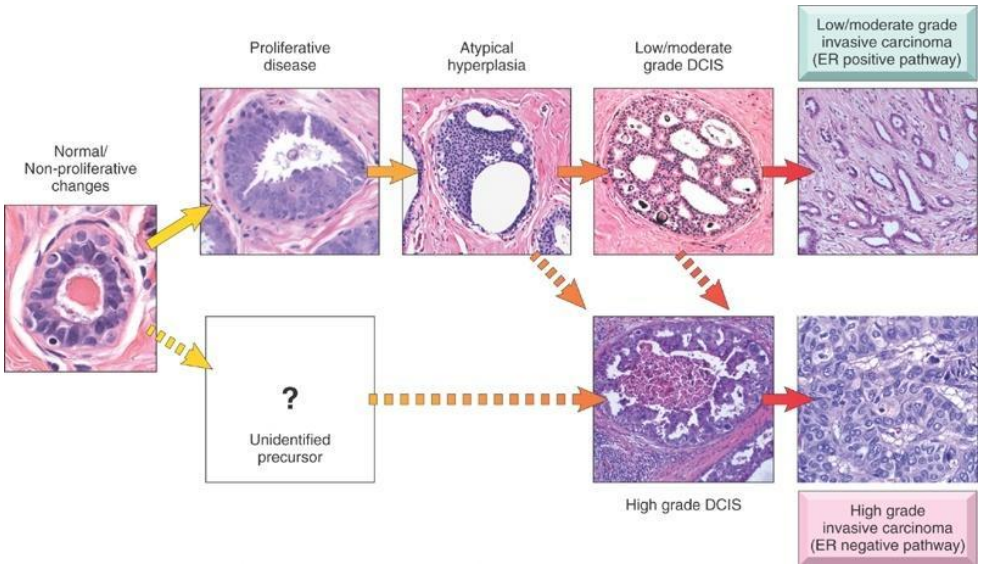


Fig.1: Proposed precursor-carcinoma sequences in breast cancer

CLINICAL PRESENTATION

50% of breast carcinoma are located in the superior & outer quadrant, 15% in the superior & inner quadrant, 10% in the inferior & outer quadrant, 5% in the inferior & inner quadrant, 17% in the central quadrant and 3% are diffuse.

CLINICAL EXAMINATION**:**

Screening for breast abnormalities are done by the triple assessment which includes clinical examination, imaging and tissue sampling.

PALPATION**:**

It remains extremely useful and is the best mode for diagnosis of breast carcinoma.

RADIOLOGICAL IMAGING:

1. **Mammogram:**

- The widespread use of mammography brought about a radical change in the diagnosis of breast cancer. [31, 32]
- Mammographic screening was first implemented in the 1980s for detecting small non palpable carcinoma that were asymptomatic.
- With increasing age, the radio dense and fibrous breast tissue of youth was replaced by the radioluscent fatty tissue that increases the mammographic specificity and sensitivity.
- The probability of mammographically detected cancerous lesion rises from 10% at 40 years to 25% at 35 years of age.

- The primary signs of mammographically detected carcinomas include density and calcification.

A. Mammographic Density

- Mammographic density is produced frequently by invasive carcinoma, fibroadenoma or cyst.
- Most tumors are denser radiologically compared to the adjacent normal breast parenchyma.
- Mammography is valuable for detecting tiny, clinically not palpable cancer.

B. Calcification:

- Calcification forms in the areas of necrosis, hyalinised stroma or secretion.
- The incidence of calcification in breast carcinoma is 50-60% [33, 34] .Whereas the incidence of calcification in benign breast disease is 20%.
- Hyalinised fibroadenomas, apocrine cysts and sclerosing adenosis are associated with benign calcification.
- Calcification in malignancy are usually tiny, numerous, irregular and clustered.
- DCIS is most frequently detected as a calcification in mammogram. They are deposited in linear branching pattern.
- Small sized Invasive Ductal adenocarcinomas rarely present with calcification unaccompanied by mammographic radiodensity. Lymph node metastasis is rare in these cases.

2. **USG:**

- It can distinguish between cystic & solid lesions.
- It can delineate the borders more precisely in case of solid masses.

3. **MRI:**

- It detects breast carcinomas by uptake of contrast agents owing to increased vascularity of the tumor.
- It is helpful for screening high risk women and those with dense breast.
- To determine the extent of involvement of chest wall by cancers that are locally advanced.
- For evaluating cases with rupture of breast implants.

TISSUE SAMPLING METHODS

- Trucut Biopsy
- Incision Biopsy
- Excision Biopsy
- Radical and Modified Radical Mastectomy
- FNAC

CLASSIFICATION OF BREAST CANCERS

Breast carcinoma is classified clinically based on tumor size, lymph node status, local extent and distant spread, morphologically based on histological type and grade, At Molecular level, according to hormone receptors and HER2neu status. WHO Classification of breast tumor is given in Annexure –I.

MOLECULAR CLASSIFICATION OF BREAST CANCER: [35, 36, 37, 38]

Luminal A:

- This phenotype is seen in 40% - 50% of the IDC NOS type cancer.
- It includes ER positive and HER2neu negative tumor.
- Most of the tumors are moderately to well differentiated with increased expression among post-menopausal female.
- These tumors are slow growing and respond well to hormonal therapy. But response to standard chemotherapy is seen in only minimal number of cases.

Luminal B:

- This phenotype is seen in 15% - 20% of IDC-NOS type cancer.
- They are triple positive tumors with expression of ER, PR & HER2neu.
- They are of higher grade with increased proliferative potential.
- Increased frequency of nodal metastasis is seen.
- Responds well to chemotherapy.

Normal Breast Like:

- This phenotype accounts for 6% - 10% of IDC NOS type cancer.
- This is a minor group consisting of well differentiated ER positive & HER2neu negative cancers. They show similar gene expression pattern like that of normal breast parenchyma.

Basal Like:

- This phenotype accounts for 13% - 25% of IDC NOS type cancer.
- These tumors are characterized by the absence of PR, ER & HER2neu expression with expression of basal myoepithelial markers like P63, P-Cadherin markers and of progenitor cells / putative stem cells (CK 5/6)
- This group is referred as "TRIPLE NEGATIVE" Carcinoma. [39, 40]
- Tumors included in this category are medullary & metaplastic carcinomas.
- Breast carcinomas harboring BRCA1 mutation usually belong to this group.
- They are of higher grade with increased proliferative potential and aggressive clinical course.
- They are frequently associated with visceral and CNS metastasis.
- Complete response following chemotherapy is seen in only 15-20% of cases.

HER2neu Positive:

- This phenotype is seen in 7% - 12% of IDC NOS cancers.
- It includes carcinomas with HER2neu over expression and ER / PR negativity.
- In 90% of cases, over expression is mainly due to amplification of the DNA segment on chromosome 17q21 that harbors the HER2neu gene and varying number of adjacent genes.
- HER2neu assay that include measurement of gene copies number by FISH, mRNA level, by gene assay and protein by IHC are all deranged in most of these cancers.
- They are generally poorly differentiated with increased proliferative potential & are associated with increased frequency of CNS metastasis.

INFILTRATING DUCTAL CARCINOMA NOS

It is the most frequent type constituting 75-80% of breast cancers. [41] Grossly, it has irregular infiltrating borders which imparts stellate appearance and has firm to hard consistency. It has abundant elastotic stroma and small foci of calcification which gives grating sound while cutting.

Microscopically, it is composed of tubules, solid sheets, nests and single cells in varying proportions depending on the degree of

differentiation. Grading of these tumors is by Nottingham Modification of Richardson System. (Annexure III).

INFILTRATING LOBULAR CARCINOMA

This tumor constitutes 10% of all breast carcinomas and it is the second commonest type of breast cancer. It has greater incidence of bilaterality and multicentricity. Grossly present as a discrete mass or diffuse indurated area.

Microscopically there is dyscohesive infiltrating tumor cells arranged in single file or in loose clusters or sheets. Genetic profile is similar to Luminal A. [42] There is characteristic loss of E-cadherin that function as tumor suppressor and biallelic loss of expression of CDH 1. [43, 44, 45]

This tumor is positive for HMWkeratin, lack of p53. [46] To these, p120 catenin has been recently added, supported by the claim that lobular carcinoma shows a characteristic cytoplasmic staining pattern with this marker. [47] Grading is similar to other breast carcinomas. [48]

MEDULLARY CARCINOMA

These tumors have basal like gene expression profile. [49] Positive for CK7 and triple negative. [50] More common in sixth decade and is associated with BRCA1 mutation. [51]

These are well circumscribed tumors and slow growing thus clinically mimicking benign lesion. Grossly, well circumscribed, soft and

fleshy. Microscopically, more than 75% of tumor is composed of solid sheets of cells with pleomorphic vesicular nucleus and prominent nucleoli admixed with lymphoplasmacytic infiltrate most of them being cytotoxic T cells. [52]

The tumor has increased mitosis and has Pushing border due to overexpression of E-cadherin and because of this, metastasis is limited. [42] There is a scant fibrous stroma with minimal glandular differentiation. All Medullary carcinomas are poorly differentiated but has better prognosis than Infiltrating Ductal Carcinomas.

MUCINOUS CARCINOMA

These tumors are common in the older age group (seventh decade) and has a variety of names like Colloid carcinoma, Mucoid carcinoma and Gelatinous carcinoma. Grossly, they are well circumscribed and appear as a gelatinous mass held by fibrous septa.

Microscopically, clusters of tumor cells float in a pool of mucin. The tumor cell clusters may be solid or exhibit acinar or micropapillary architecture. [53] When mucin forms more than 90% of tumor content, it is called Pure mucinous carcinoma, Otherwise it is called Mixed mucinous carcinoma.

The mucin in the tumor is extracellular and acid or neutral type. [54] Histochemically, they are O-acylated forms of Sialomucin. [55] They are

strongly positive for MUC2. [56] These tumor cells are ER, PR positive and HER2neu negative. [57]

APOCRINE CARCINOMA:

This is a rare tumor type constituting 1-4% of breast carcinomas. In this tumor more than 90% of tumor cells are of apocrine cells. [58]

Microscopically, there are two types of apocrine cells. Type A cells with abundant acidophilic granular cytoplasm and Type B cells with clear foamy cytoplasm. There is glandular differentiation with characteristic apocrine snouts. These tumors are positive for Androgen receptor and negative for ER, PR and BCl2.

METAPLASTIC CARCINOMA

This is a rare tumor subtype with predominant component of tumor has an appearance other than epithelial and glandular type. [59, 60] Microscopically, it is composed of heterogeneous components like Spindle, squamous, mesenchymal elements like osseous and chondroid material in varying proportions.

This category also includes Matrix producing carcinoma in which there is overt transition from carcinoma to cartilaginous or osseous matrix without spindle transition zone. [61, 62] It has basal like gene profile with infrequent lymph node metastasis.

TUBULAR CARCINOMA

These tumors are common around 50 years of age. Grossly, they are small with ill-defined margin and hard consistency. Microscopically, there is irregular and angulated glands arranged haphazardly in a desmoplastic stroma.

Low grade DCIS and Flat epithelial Atypia are considered to be precursor lesions for this carcinoma.

CRIBRIFORM CARCINOMA

These are rare tumors in which more than 90% of tumor cells are arranged in sieve like cribriform pattern similar to insitu counterpart but with stromal invasion.

INVASIVE PAPILLARY CARCINOMA

These tumors constitute less than 1% of breast carcinoma. They are circumscribed tumors in which cells arranged in delicate blunt papillae and myoepithelial cells are absent. It has better prognosis than conventional IDC NOS

INVASIVE MICROPAPILLARY CARCINOMA

This category constitutes less than 2% of breast carcinoma. These tumors have pseudopapillary structures without fibrovascular core. These are high grade tumors, highly invasive and can have psammoma bodies. [63]

NEUROENDOCRINE CARCINOMA

This term indicates invasive tumors that exhibit neuroendocrine differentiation. [64] It includes Carcinoid, Large cell neuroendocrine and small cell neuroendocrine carcinoma. Microscopically, solid nests of small cells separated by fibrous stroma.

It can be distinguished from breast carcinoma with focal endocrine differentiation by IHC which shows expression of neuroendocrine markers in more than 50% of tumor cells. [65]

INFLAMMATORY CARCINOMA

This category has its name because clinically it presents as a red warm breast with widespread edema. Pathologically, it presents as undifferentiated carcinoma with lymphatic permeation.

Skin biopsy demonstrates the presence of dermal lymphatic invasion. It is an ominous sign for occult inflammatory carcinoma. [66]

PROGNOSTIC FACTORS

Prognostic information is important in counseling patients about the likely outcome of the cancer, and appropriate treatment.

AGE OF THE PATIENT

Prognosis is better when the patient is less than 50 years of age. Prognosis declines after 50 years of age.

SIZE

Size is an important prognostic factor and studies shows good correlation between nodal status and survival rate. [67, 68] Size is one of the two criteria for the definition of minimal breast carcinoma, which includes all insitu carcinomas regardless of size and invasive carcinomas of <1cm in diameter.

SITE

Tumors located in the medial quadrant were associated with higher risk of (50%) relapse and tumor-related death than laterally located tumor. [69]

CYTOARCHITECTURAL TYPE

There is no significant difference in prognosis between ordinary invasive ductal and lobular carcinoma. [70] Morphological variants like Tubular, Mucinous, Medullary, Papillary, Cribriform, Adenoid cystic carcinoma and Secretary Carcinoma have good prognosis. [71]

Variants like Inflammatory, Metaplastic, Squamous cell carcinoma, Neuroendocrine and Signet ring cell carcinoma are aggressive tumors with bad prognosis. [72]

PRESENCE OR ABSENCE OF INVASIVENESS

In tumors of ductal type that have both in situ & invasive component, a relationship exists between the proportion of the invasive component and the probability of nodal metastasis.

The amount of insitu component correlates with the incidence of multicentricity and indirectly with the probability of occult invasion. [73].

In situ ductal malignancies of the comedocarcinoma type can be associated with metastases in the absence of detectable invasion.

TUMOR NECROSIS

Spontaneous tumor necrosis is associated with an increased nodal metastases & reduced survival rates, [74] particularly if very extensive. This feature is usually associated with tumors of high histologic grade. [75]

TYPE OF MARGINS

Tumors with infiltrating margins have a worse prognosis than tumors with pushing margins. [76, 77]

MICROSCOPIC GRADE

Grading is based on Nottingham Modification of Scarff Bloom Richardson system (Annexure III). [53] Ellis et al established that there is an

excellent correlation between this grading system and patient's survival and rate of metastasis. [29]

SKIN INVASION

Breast carcinomas with infiltration of the overlying skin are associated with decreased survival rate. [78]

NIPPLE INVASION

Involvement of nipple by carcinomas is associated with higher incidence of axillary metastasis. [79]

BLOOD VESSEL EMBOLI

This finding shows a high correlation with histological grade, size of tumor, type of tumor, lymph node status and Development of distant metastasis. Vascular invasion is associated with poor prognosis. [80]

LYMPHATIC TUMOUR EMBOLI

Presence of tumor emboli in lymphatic vessels within the breast is associated with more risk of tumor recurrence. [81, 82]

LYMPH NODE STATUS

Axillary lymph node involvement is an important prognostic factor in patients without distant metastasis. Number of axillary nodes involved, level of the node and amount of tumor cells in the node, presence or absence of tumor crlls in the efferent blood vessels have important implication in patient's survival. [83]

METASTASIS

Locally advanced disease and presence of distant metastasis have poor prognosis. The timing and location of metastasis is also influenced by the tumor type. [84, 85]

BRCA-1 STATUS

The Breast carcinomas developing in BRCA 1 mutation carriers are associated with overall poor survival, if they have not received adjuvant ftherapy. [86] Absent (or) reduced nuclear BRCA 1 expression as measured immunohistochemically is associated with several microscopic unfavorable features and shorter disease free intervals, whereas cytoplasmic expression of this marker seems to be associated with development of tumor recurrence. [87]

STAGING (TNM) **(Annexure VI)**

PROLIFERATION RATE

The proliferation rate is measured by mitotic counts, IHC detection of cellular proteins like Cyclins, Ki67, and flow cytometry. High proliferation rate is associated with poor prognosis but the response to chemotherapy is better. It can also be measured by (SPF) S-Phase fraction and thymidine labeling index. Tumors with SPF <5% showed a response rate of 46%, those with SPF of 5-10% showed 84% response and those with high SPF >10% showed 100% response.

OTHER PROGNOSTIC FACTORS

Many factors like Tumor necrosis, Lymphocytic infiltration, Skin infiltration, association with pregnancy and lactation, [88] BRCA mutation, [89] vimentin and keratin expression [90] also have variable prognostic implications in breast cancer.

HORMONE RECEPTORS

Breast cancer cells generally express ER, PR as well as Human Epidermal Growth Factor Receptor (HER2neu) for breast cancer formation and its progression.

IHC was discovered 30 years back which was used to classify breast cancers. IHC to detect nuclear hormone receptors is correlated with better outcome and predict response to hormonal therapy. [91, 92]

Hormone receptor expression was initially measured by Dextran coated charcoal and sucrose gradient assay and it was now replaced by IHC and a very good correlation was established between these methods. [93, 94] ER positive cancer cells depend on estrogen for their growth and hence antiestrogenic agents (eg. Tamoxifen) inhibit cell proliferation. [95, 96]

ER and PR are coindependent variables. ER being a better predictor of response to hormone therapy than PR. [97] HER2neu positive tumors have worse prognosis in spite of showing good response to Monoclonal antibody

Transtuzumab. [98] It can be measured by IHC or FISH and better correlation exists with these methods. [99, 100]

Fisher et al proposed that presence of ER is significantly associate with high nuclear grade, absence of necrosis, marked tumor elastosis and older age group. [101]

Shorlie et al and Person et al demonstrated the "Heat maps" generated by microarray technique was used to find the expression pattern of 426 genes. [102] These leads to sub classification of breast tumors. [101] IHC has become surrogate for DNA microarray gene expression classification. [66]

Harvey et al in 1999 suggested cut off values for ER/PR score for treatment of advanced stage disease.

0 score = Endocrine therapy will definitely not work.

2-3 score = 20% possibility of response to therapy.

4-6 score = 50% possibility of response to therapy.

7-8 score = 75% possibility of response to therapy.

SIGNIFICANCE OF HER2NEU IN BREAST CANCER

About one fourth of primary or metastatic breast cancers over express HER2neu. As a result, some breast cancers that are ER positive also are HER2neu positive.

Recent observations have demonstrated that ER positive, HER2neu positive metastatic human breast cancers are less likely to respond to

hormone therapy than are cancers that are only ER positive. This is consistent with the in vitro observation that MCF cells (ER positive) become resistant to tamoxifen after they are transfected with the HER2neu oncogene.

HER2neu activation can result in an alteration of the ER.

Treatment of cells that over express HER2neu with Estrogen, decreases HER2neu mRNA, as well as down regulating the HER2neu product.

Conversely treatment of ER positive cells with HER2neu ligand leads to decreased ER expression.

This cross link between a polypeptide growth factor receptor – activated pathway and a hormone receptor pathway appears to be a mechanism by which the cell can become hormone independent.

TRIPLE NEGATIVE BREAST CANCER

The cancer which is negative for Hormone receptors ER and PR and HER2neu is called Triple negative Breast cancer. This means that these tumor growth is not supported by Estrogen and Progesterone Hormones and do not have many HER2neu receptors. So they do not respond to the treatment by Tamoxifen nor to therapies that target on HER2neu receptors (Tanstuzumab).

This category incites an interest to Doctors and Researchers in finding therapies that interfere with the growth process of HER2neu receptors. The triple negative tumors are generally more aggressive tumors, higher grade than other breast carcinomas and express basal like markers like CK5/6, P53.

It is more common in younger age group especially before 40yrs of age and more common in patients with BRCA1 mutation.

Triple negative breast cancers are typically treated with multimodality therapy using surgery, Radiotherapy and Chemotherapy. Some research showed that Triple negative cancers actually showed a better response to Chemotherapy than other breast cancers.

IMMUNOHISTOCHEMISTRY

Immunohistochemistry was first described by Dr. Albert Coons in 1941. Since then numerous advancements in the technique have been made. [103] The most commonly used technique is the Peroxidase-antiperoxidase immune complex method developed by Sternberger in 1970. The newer biotin-avidin immunoenzymatic technique was developed by Heitzman and Richards in 1974. [104, 105]

USES OF IHC IN BREAST PATHOLOGY

1. The use of Myoepithelial markers to assess stromal invasion.
2. To differentiate between different types of breast cancer. Eg. E-cadherin helps to differentiate between ductal and lobular carcinoma.
3. To differentiate between precursor lesions and malignancy. Eg. HMWCK helps to distinguish between Usual Ductal Hyperplasia and Ductal carcinoma insitu.
4. To find the site of origin in metastatic cancers.

5. To detect sentinel lymphnode metastasis.
6. Assessment of Estrogen and Progesterone receptor status and HER2neu overexpression using specific antibodies to receptor proteins.
7. Evaluation of Metaplastic carcinoma from mesenchymal lesions.

ANTIGEN RETRIEVAL

Shi et al developed the antigen retrieval technique in 1991 in which high temperature was used to bring out the antigenicity of the tissues which had been masked by formalin fixation. Antigen retrieval is done either by heat induced epitope retrieval or proteolytic epitope retrieval.

HEAT INDUCED

The tissue sections are placed in retrieval solution and subjected to heat for varying periods of time. This breakdowns the protein crosslinks and retrieves antigenicity. [106] The heat can be applied using microwave oven, pressure cooker, steamer, autoclave or water bath. The commonly used retrieval solutions are citrate buffer at PH 6, TRIS EDTA at PH 9, EDTA at PH 8.

PROTEOLYTIC EPITOPE RETRIEVAL [107]

Tissue antigenicity can also be restored using proteases like Proteinase K, trypsin, Chymotrypsin and pepsin. The main disadvantage here is it alters tissue morphology and destroys some epitopes.

TARGET ANTIGEN DETECTION METHODS

After retrieval specific antibodies are added which forms Antigen antibody complex. This can be visualized by Direct and Indirect methods.

DIRECT METHOD

Her labeled antibodies are used which react with antigens in tissue sections. Some of the labels are fluorochrome, horse radish peroxidase and alkaline phosphatase. It is simple and rapid but has low sensitivity.

INDIRECT METHOD

Here, in the first step unlabeled primary antibody is added which binds with the target antigen. Then in the second step, a labeled secondary antibody is added which react with the primary antibody. It is more sensitive and it uses only a small number of secondary antibodies. [108]

ANDROGEN RECEPTOR

Androgen receptor belongs to a member of nuclear steroid hormone receptor superfamily and it shares many structural, functional and topographic similarity to Estrogen and Progesterone receptors. [109, 110, 111] AR has an important role in the normal development of Prostate and in the pathogenesis of Prostatic carcinoma. It also has a role in breast cell differentiation, development and growth. In prostate cancer, AR dependent cell cycle progression appears to be a critical regulator in G1-S transition. In

breast cancer also similar role has been envisaged. It is considered as a newly emerging biomarker in breast carcinoma. [112]

Androgen Receptor plays a crucial role in breast homeostasis, negatively influences the proliferative effects of Estrogen signaling. It also influences the risk of breast cancer by converting into estradiol which acts on Estrogen or Androgen receptor in breast.

Peters et al assessed status of Androgen receptor in 215 cases of breast cancer and found that by binding to a subset of Estrogen responsive element. AR can block the target gene that mediates the stimulatory effects of 17β estradiol on breast cancer.

A cell line model for molecular apocrine subtype MDA-MB-453 demonstrates a proliferative response to androgen in an ER independent manner. [113] And it can be reversed using antiandrogen Flutamide.

The antiandrogen Bicalutamide also inhibits the growth of molecular apocrine cell lines in-vitro and in-vivo supporting the fact that antiandrogen can be used as a targeted therapy. [113, 114,115,116]

Various studies show variable results regarding the significance of AR expression in breast cancer. Agarwal et al showed that AR is the most frequently detected receptor in breast cancer. [117]

Agoff SN et al showed that most breast cancer cells have receptors for androgen and it may be found in the absence of ER and PR especially in the

absence of ER. [118, 119] Many studies have shown that AR expression is more frequent in Lobular carcinoma, Apocrine carcinoma and Paget's disease of nipple. [120, 121, 122]

Literature has shown that DHEA and its sulfate has growth inhibitory effects on Estrogen and Progesterone receptor negative breast cancer lines that show AR expression. [123, 124]

Leo A Neiemeier et al showed AR positivity in 80% of invasive breast carcinomas and 95% of ER positive breast carcinomas and 10% of triple negative breast carcinomas. [125]

Park et al found AR positivity in 58% of breast carcinomas and 35% of triple negative breast carcinomas and it is 72.9% higher than those of ER.[126]

Dawn R Cochrane et al indicated AR positivity in 77% of breast cancers and 88% of ER positive, 59% of HER2neu positive and 32% of triple negative breast cancers. [127]

Hu R et al showed that AR is reported in almost 56% of patients with ER negative breast carcinomas. [128] Literaturealso showed that AR can be an independent prognostic factor with 61% expression in basal like breast cancer which has poor prognosis. [121]

Dawn R Cochrane et al also showed that AR expression is associated with 4 fold increased risk of tamoxifen failure. So AR had an independent

effect on risk for failure with hormone therapy. [127] AR:ER ratio is also an independent predictor of disease free survival.

Mishra et al shows that the breast cancers whish show AR expression have prolonged survival and better response to hormonal treatment than AR negative cases. [130]

Francisco et al did a Meta-analysis of 19 studies and showed that AR expression was documented in 60.5% of cases and concluded that ER positive tumors are more likely to express AR than ER negative tumors. And show improved overall survival.

MATERIALS AND METHODS

This study is a descriptive prospective and retrospective study of Primary breast carcinomas conducted in the Institute of Pathology, Madras Medical College and Rajiv Gandhi Government General hospital, Chennai during the period between Jan 2013 to Jun 2015.

Source of data

The invasive ductal carcinoma cases reported in mastectomy specimen received in the Institute of Pathology, Madras Medical College between Jan 2013 to Jun 2015 from the Department of Surgery, Oncology, and Plastic surgery, Government General Hospital. A total of 364 mastectomy specimens (simple, modified radical or radical mastectomy) were received during this period.

Inclusion criteria:

- All modified radical mastectomy specimens of breast carcinomas.
- All invasive breast carcinomas no special type (ductal and lobular), medullary, mucinous, papillary, apocrine and metaplastic carcinomas irrespective of the age and sex were included for the study.

Exclusion criteria:

- All Trucut biopsies.
- Phylloides tumors.
- Benign breast lesions.

- Tumors with preexisting premalignant conditions.
- Recurrent tumors.

METHOD OF DATA COLLECTION

Of the total 364 cases reported during this study period, ER, PR and HER2neu expression was studied for 212 cases. Detailed history of the cases regarding age, sex, menstrual history, side of the breast, type of procedure, history of neo adjuvant therapy, details of gross characteristics such as tumor size, nodal status details were obtained for those 212 cases from surgical pathology records. Formalin fixed tissue were cut, processed and paraffin embedded.

4μm thick sections of the paraffin tissue blocks were cut and stained with eosin and hematoxylin. Slides were collected from slide filing and were reviewed and graded using the Nottingham modification of the Scarff Bloom Richardson Grading system (Annexure III) and they were further evaluated for the presence of necrosis, lymphocytic response, lymphovascular invasion and skin infiltration . 10 cases of each grade from Invasive ductal carcinoma NST and 20 cases from special type as medullary, metaplastic, mucinous, apocrine, papillary and invasive lobular were randomly selected from the total cases and their representative formalin fixed paraffin embedded tissue samples were subjected to immunohistochemical analysis of Androgen Receptor. Slides were evaluated and scoring was given. The results were recorded with photographs.

IMMUNOHISTOCHEMICAL EVALUATION

Immunohistochemical analysis of ER, PR, H2N and AR were done in Paraffin embedded tissue samples using supersensitive polymer HRP system based on non-biotin polymeric technology.

Table 1: Immunohistochemical markers used in the current study

Antigen	Vendor	Clone	Dilution	Positive
ER	Dako	Rabbit Monoclonal	Ready to Use	Breast
PR	Dako	Mouse Monoclonal	Ready to Use	Breast
HER2neu	Dako	Rabbit Monoclonal	Ready to Use	Breast
AR	PathnSitu	Rabbit Monoclonal	Ready to Use	Prostate

4 μm thick sections from selected formalin fixed paraffin embedded tissue samples were transferred onto gelatin coated slides. Heat induced antigen retrieval was done using microwave method. The ER and PR antigens are bound with mouse monoclonal antibodies (dako) and HER2neu(dako) and AR(PathnSitu) antigens are bound with rabbit monoclonal antibody. Later antigen antibody complex are detected by the addition of secondary antibody conjugated with horse radish peroxidase-polymer and Diaminobenzidine substrate. The step by step procedure of Immunohistochemistry is given in Annexure IV.

INTERPRETATION & SCORING SYSTEM

PR and AR

Hormone receptors like Estrogen and Progesterone receptor, when expressed show a nuclear positivity. The number of cells expressing and their intensity of staining is scored as two values and a composite score based on percentage plus intensity of more than 2 is considered to be positive. (Annexure V).

H2N:

HER2neu expression is demonstrated in tumor cells as cytoplasmic expressing is graded as 1+, 2+ and 3+. (Annexure V)

STATISTICAL ANALYSIS

The Statistical analysis for this study was done using the software IBM Statistical Package for social science version 21. The correlation between AR expression and different clinicopathological parameters like age group, size, side, grade, lymphnode status, lymphovascular invasion, lymphocytic infiltration, necrosis, skin infiltration, Hormonal receptors like ER, PR and HER2neu was made and strength of association was calculated by Pearson Chi square test and P value less than 0.05 are considered statistically significant.

OBSERVATION AND RESULTS

In the study period of 30 months from Jan 2013 to June 2015, a total of 27,576 specimens were received in the Institute of Pathology, Madras Medical College for histological examination.

Total numbers of breast specimens received were 1515 cases, of these breast tumors accounted for 1145 cases with a percentage of 4.15% of all cases (including both incisional and excisional biopsies).

The total number of non-neoplastic, benign and malignant cases was 370, 484 and 661 respectively. Thus the distribution of non-neoplastic breast lesions was 24.42%, benign tumors were 31.95% and of malignant tumors were 43.63%.

Out of a total of 661 breast cancer cases, only 364 cases constituted radical mastectomy specimens.

Table 2: Distribution of breast cases

	Non neoplastic	**Benign**	**Malignant**
Breast	370	484	661

The age wise distribution of these 212 cases is given below (Table 3 and Chart 1)

Table 3: Age Wise Distribution Of Breast Cancers

AGE	NO OF CASES	PERCENTAGE
21-30	3	1.41%
31-40	37	17.45%
41-50	83	39.15%
51-60	63	29.71%
61-70	23	10.85%
MORE THAN 70	3	1.41%
TOTAL	212	100%

Highest incidence of Breast cancers is found in the age group of 41-50 years. The youngest age of presentation of breast cancer is at 30 years in this study.

The distribution of histological subtypes of breast carcinoma is shown (Table 4, chart 2).

Chart 1: Age distribution of Breast cancers

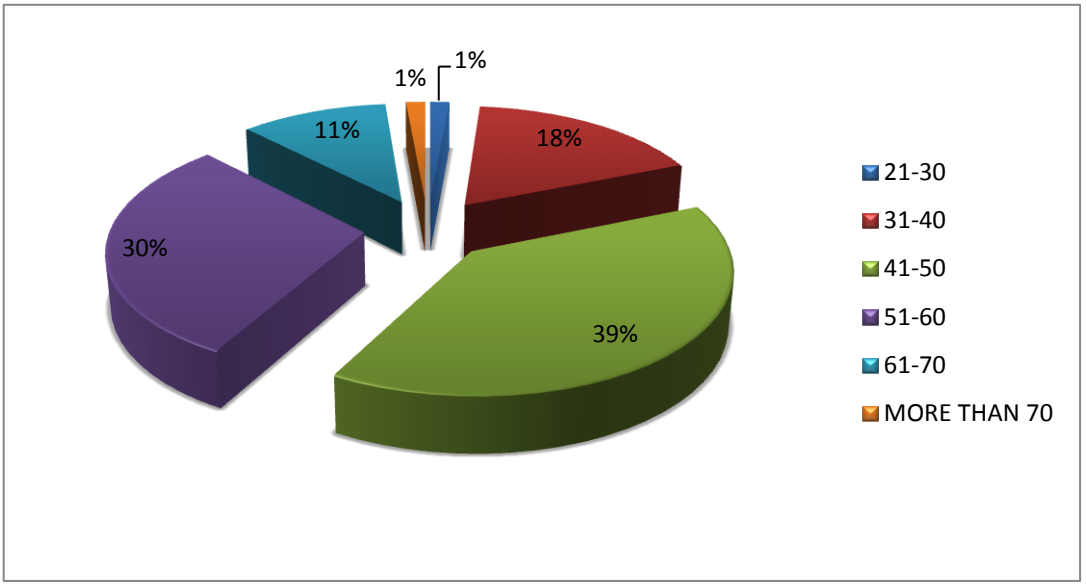


Table 4: Distributions of Histological Subtypes of Breast Cancers

HISTOLOGICAL SUBTYPES	NO OF CASES	PERCENTAGE
Invasive ductal carcinoma NOS	190	89.62%
Metaplastic Carcinoma	6	2.83%
Mucinous Carcinoma	5	2.36%
Apocrine Carcinoma	4	1.89%
Invasive Lobular Carcinoma	3	1.42%
Medullary carcinoma	2	0.94%
Neuroendocrine carcinoma	1	0.47%
Invasive Papillary carcinoma	1	0.47%
Grand Total	212	100.00%

Invasive Ductal carcinoma constitutes the most common carcinoma with 89.62% of all cases.

Chart 2: Distribution of histological type

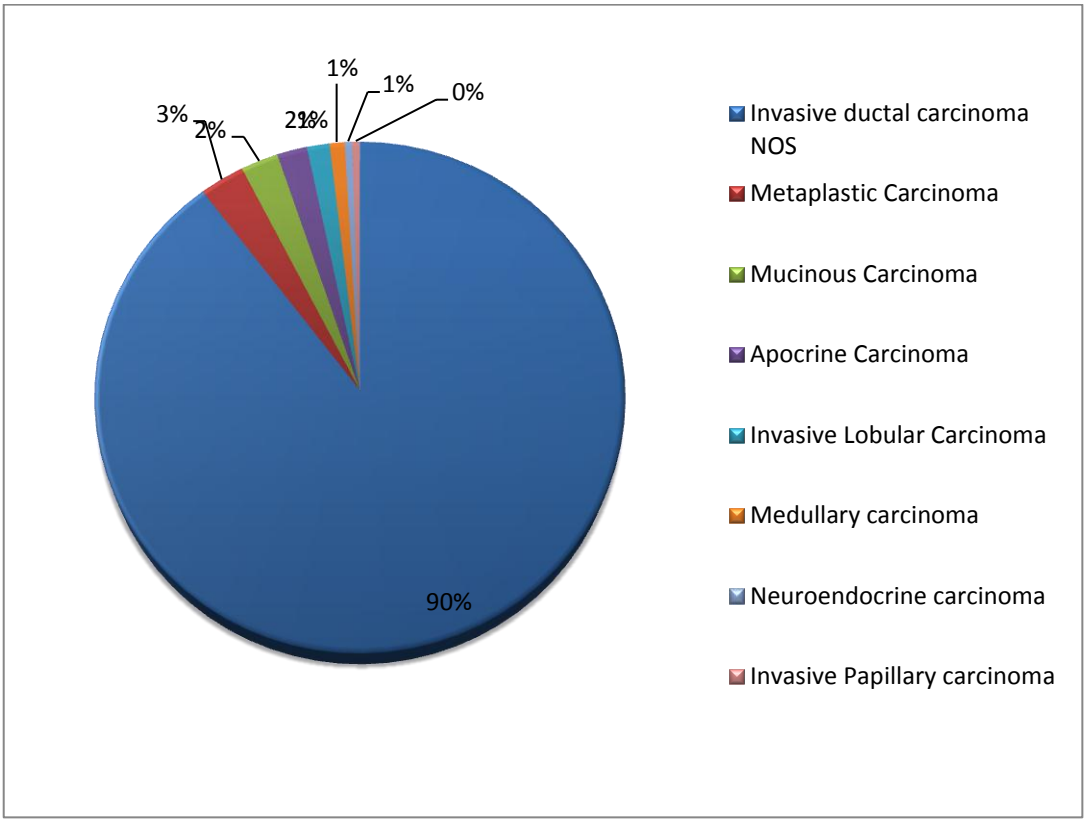
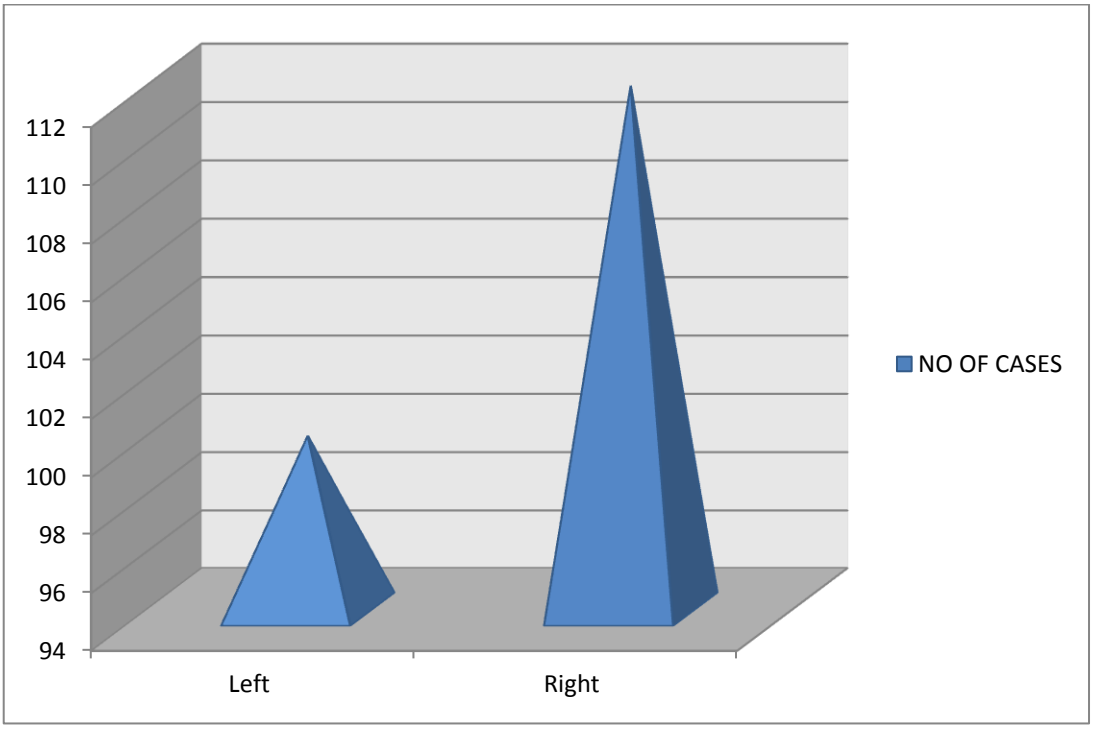


Table 5: Distribution of side of involvement in Breast

SIDE	NO OF CASES	PERCENTAGE
Left	100	47.17%
Right	112	52.83%
Grand Total	212	100.00%

Chart-3: Distribution of side of cancer



100 cases of primary breast carcinoma were reported in left breast and 112 cases were reported in right Breast. (Table 5 and Chart 3)

Table 6: Distribution of size in Invasive Ductal Carcinoma

SIZE OF TUMOR	NO OF CASES	PERCENTAGE
<2cm(T1)	9	4.25%
2-5cm(T2)	149	70.28%
>5cm(T3)	54	25.47%
TOTAL	212	100.00%

9 cases (4.25%) had tumor less than 2 cm in size, 149 cases (70.28%) were of 2 to 5 cm in size and 54 cases (25.47%) were more than 5 cm in size. (Table 6 & Chart 4).

Chart-4: Distribution of size of the tumor

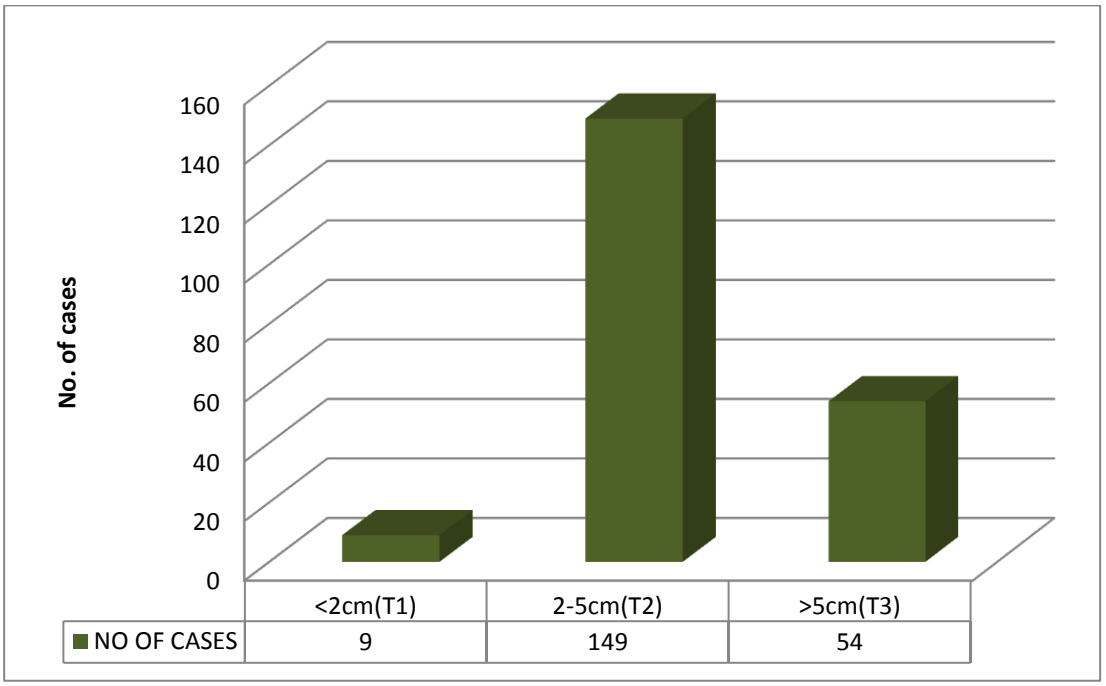


Table 7: Distribution of Histological Grade in IDC-NOS Type

GRADE	NO OF CASES	PERCENTAGE
I	38	20.00%
II	118	62.11%
III	34	17.89%
Grand Total	190	100.00%

There were 190 Invasive ductal carcinoma NOS type breast cancers in the study sample which were graded according to Modified Scarff Bloom Richardson grading system out of which 38 cases(20%) were in grade I, 118 cases (62.11%) were in grade II and 34 cases (17.89%) were in grade III. (Table 7 & Chart 5)

79 cases (37.26%) had up to 3 nodes with metastatic ductal carcinomatous deposit, 41 cases (19.34%) had 4 to 10 involved nodes, 9 cases (4.2%) had more than 10 involved nodes, while 83 cases (39.15%) had no lymph node involvement (Table 8 & Chart 6).

Table 8: Distribution of Lymph Node Metastasis in Breast Cancers

LYMPH NODE STATUS	NO OF CASES	PERCENTAGE
Negative	83	39.15%
1-3 positive nodes	79	37.26%
4-10 positive nodes	41	19.34%
>10 positive nodes	9	4.25%
Total	212	100.00%

Chart-5: Distribution of grade in IDC-NOS

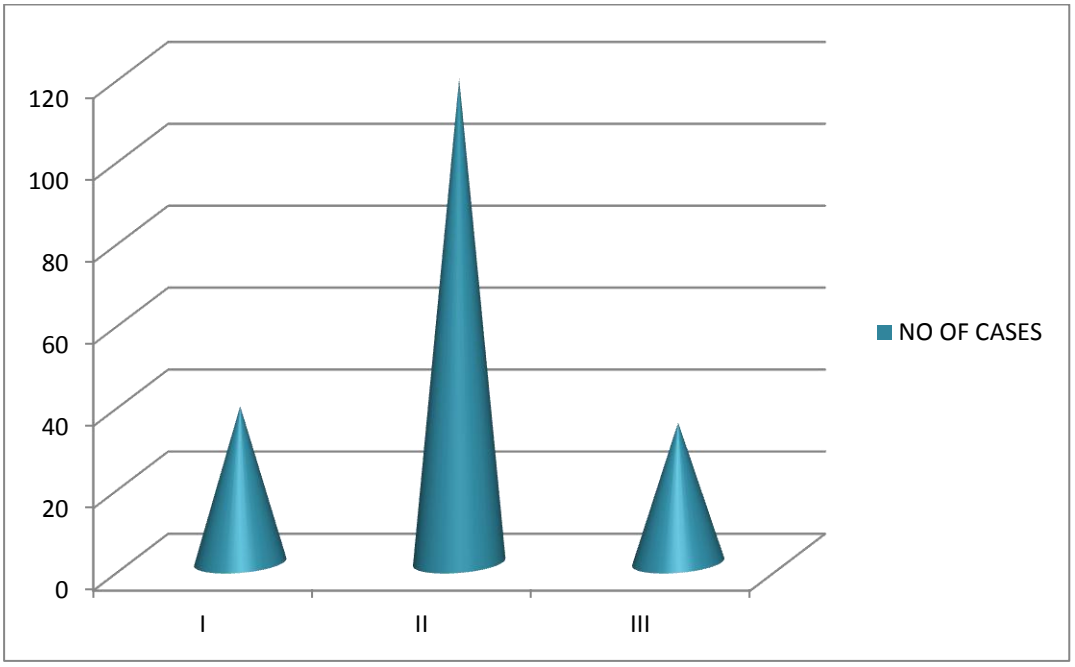


Chart 6 : Distribution of Nodal Metastasis

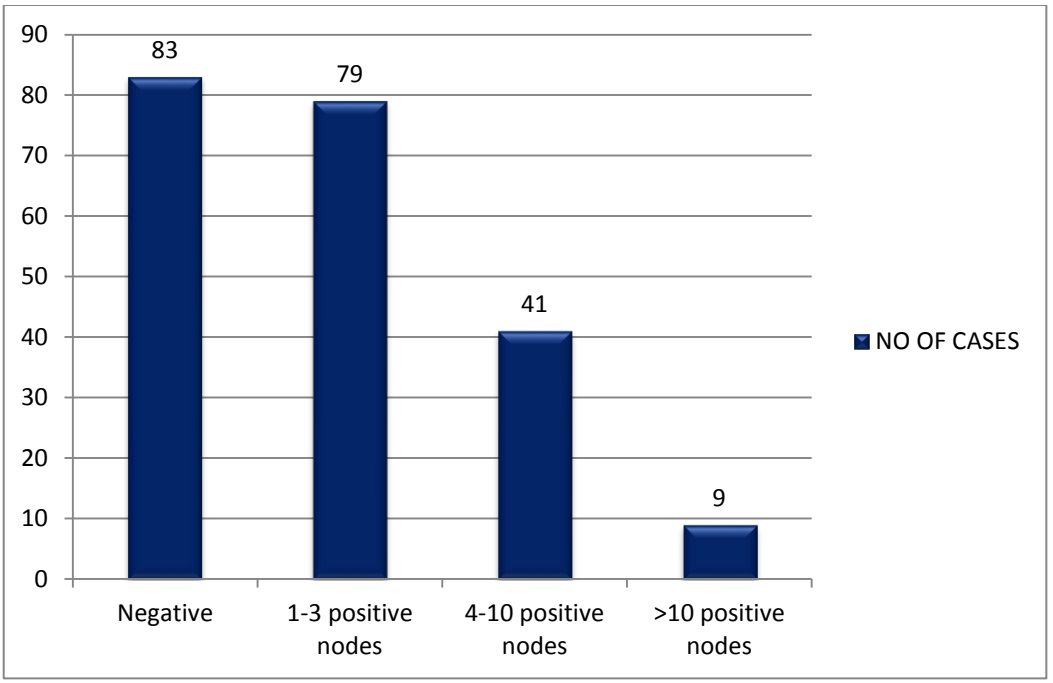


Table 9: Distribution of lymphovascular invasion

LYMPHOVASCULAR INVASION	NO OF CASES	PERCENTAGE
ABSENT	113	53.30%
PRESENT	99	46.70%
TOTAL	212	100.00%

99 cases (46.70%) had lymphovascular invasion as against 113 cases (53.3%) without lymphovascular invasion (Table 9 & Chart 7).

17 out of 212 primary breast cancers have skin infiltration which constitutes 8.02% (Table 10 & chart 7).

Table 10: Distribution of skin infiltration in Invasive Ductal Carcinoma Breast

SKIN INFILTRATION	NO OF CASES	PERCENTAGE
ABSENT	195	91.98%
PRESENT	17	8.02%
TOTAL	212	100.00%

Chart 7: Distribution of Lymphovascular invasion and Skin infiltration

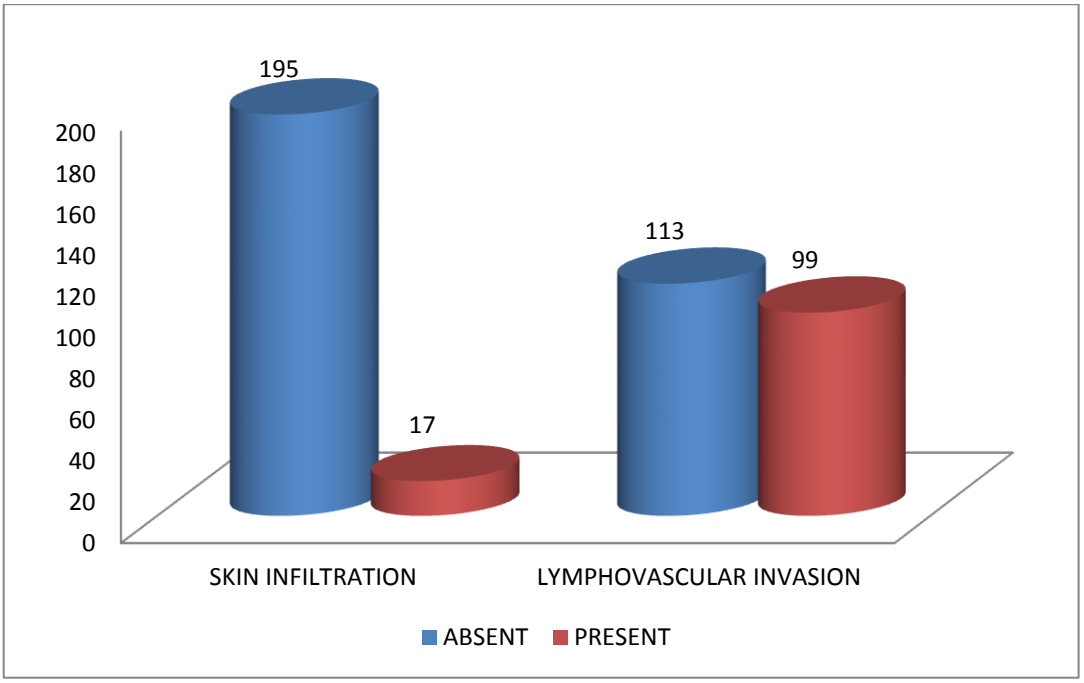


Chart 8: Distribution of Lymphocytic infiltration & Necrosis

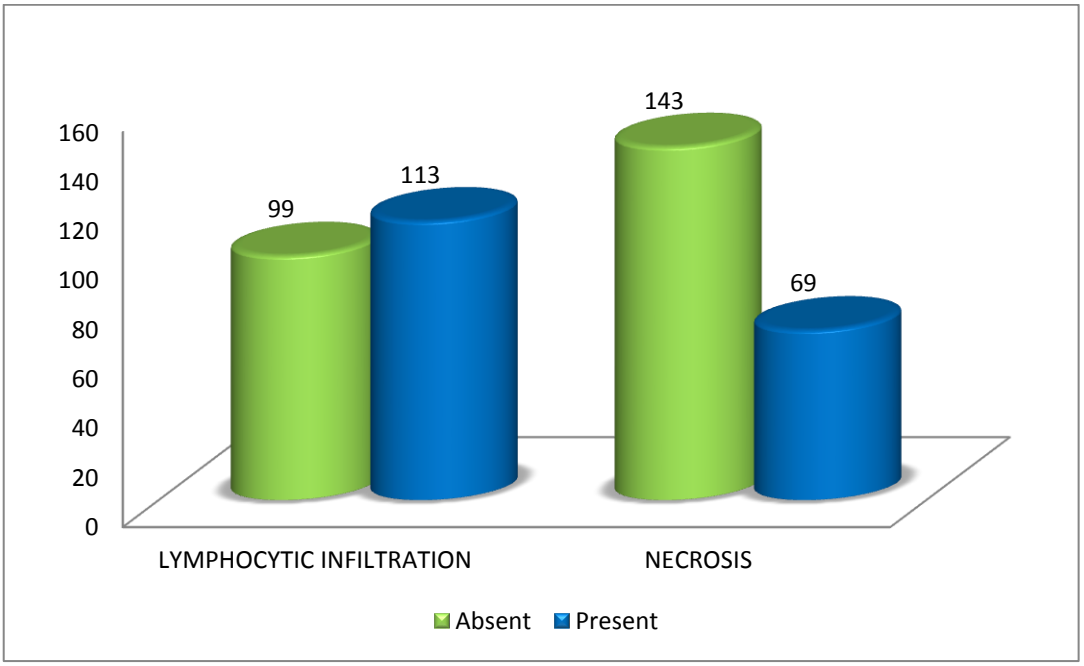


Table 11: Distribution of lymphocytic infiltration in Invasive Ductal Carcinoma Breast

LYMPHOCYTIC INFILTRATION	NO OF CASES	PERCENTAGE
Absent	99	46.70%
Present	113	53.30%
Total	212	100.00%

Lymphocytic infiltration is seen in 113 cases which forms 53.3% of all cases (Table 11) and 32.55% of the cases had necrosis (Table 12) as shown in Chart 8.

Table 12: Distribution of necrosis in Breast Cancer

NECROSIS	NO OF CASES	PERCENTAGE
Absent	143	67.45%
Present	69	32.55%
Grand Total	212	100.00%

RESULTS OF IMMUNOHISTOCHEMISTRY

Table 13: Distribution of Estrogen Receptor expression in Breast cancers.

ER	NO OF CASES	PERCENTAGE
NEG	103	48.58%
POS	109	51.42%
Grand Total	212	100.00%

IHC scoring of ER and PR done using Alred scoring system based on staining intensity and proportion of cells exhibiting positivity shows 103 cases of ER positivity which forms 51.42% of cases (Table 13) whereas PR expression is seen in 99 cases which constitute 46.7% of cases (Table 14, chart 9).

Table 14: Distribution of Progesterone Receptor Expression in Breast cancers.

PR	NO OF CASES	PERCENTAGE
NEG	113	53.30%
POS	99	46.70%
Grand Total	212	100.00%

Chart 9: Expression of ER and PR in primary Breast cancers.

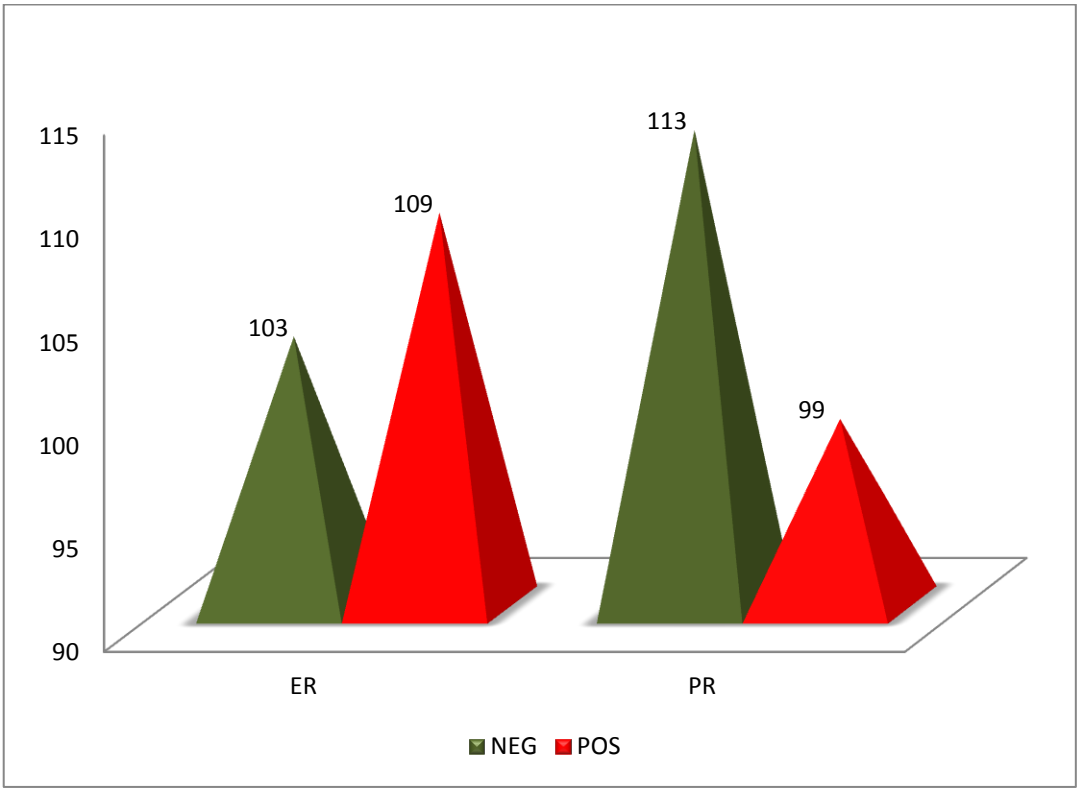
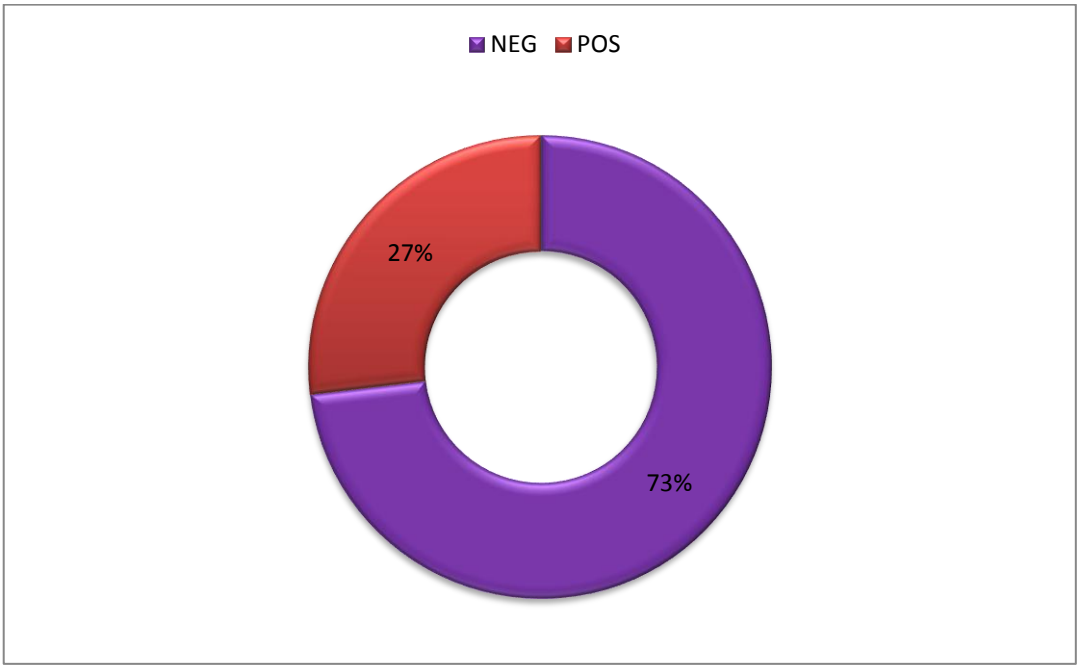


Chart -10: Expression of HER2neu



156 cases (73.58%) were Positive for HER2neu (Table 15, chart 10)

Table 15: Distribution of HER2neu expression in Breast cancers.

H2N	NO OF CASES	PERCENTAGE
NEG	155	73.11%
POS	57	26.89%
Grand Total	212	100.00%

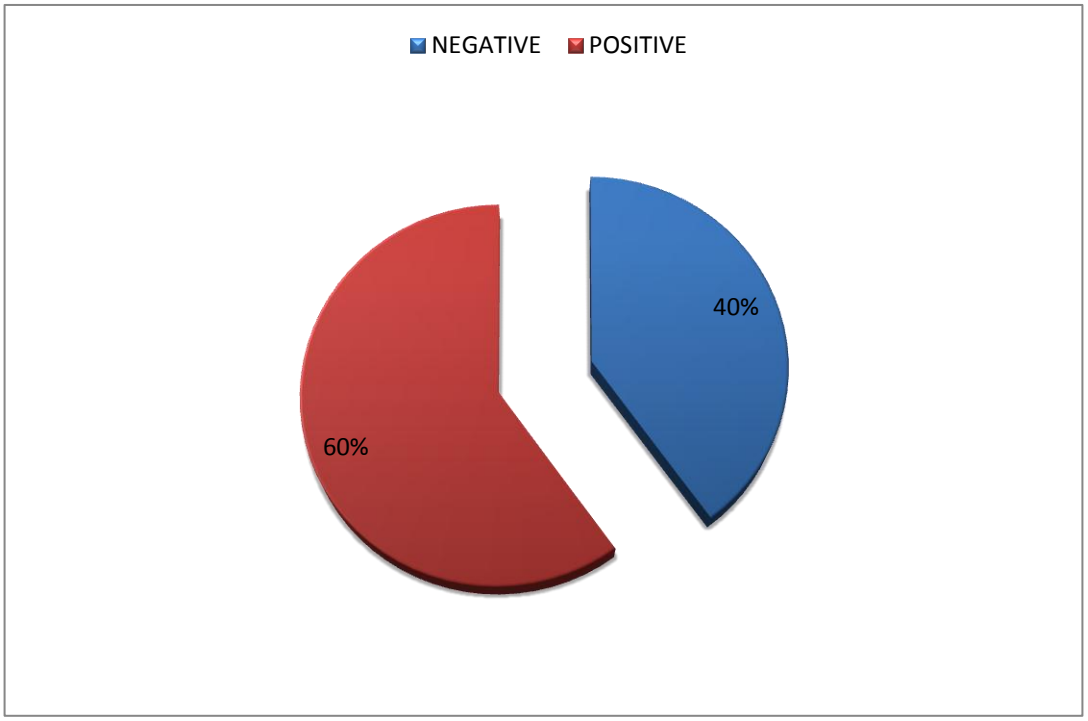
EXPRESSION OF ANDROGEN RECEPTOR

In this study, 60% expressed positive reaction for AR (Table 16 & Chart 11)

Table-16: Distribution of Androgen Receptor expression in Breast cancers.

DISTRIBUTION OF AR	NO OF CASES	PERCENTAGE
NEG	20	40%
POS	30	60%
Grand Total	50	100%

Chart-11: Expression of AR



CORRELATION OF AR WITH OTHER PROGNOSTIC FACTORS

Table-17: Correlation of Age distribution and Expression of Androgen Receptors

Age	AR expression		total	P value
	Positive	Negative		
21-30	1(50%)	1(50%)	2	0.260728
31-40	4(66.7%)	2(33.3%)	6	
41-50	6(37.5%)	10(62.5%)	16	
51-60	12(66.7%)	6(33.3%)	18	
61-70	6(85.7%)	1(14.3%)	7	
MORE THAN 70	1(100%)	0(0%)	1	
TOTAL	30	20	50	

Expression of Androgen receptor is more in the age group of 61-70 years with 85.7% positivity and one case over 70 years is positive for AR. The least AR positivity is seen in the age group of 41-50 years with 37.5% of cases although it is not significant. (Table 17 & Chart 12).

Androgen receptor is seen 100% cases of Apocrine carcinoma, Lobular carcinoma and Neuroendocrine carcinoma eventhough the size of sample is very small whereas AR is absent in 100% cases of Medullary and Papillary carcinoma. In Infiltrating Ductal Carcinoma and Mucinous carcinoma it is

seen in 60% of the cases. But these results are not statistically significant. (Table 18 & Chart 13)

Table-18: Correlation of Histological Types and Expression of Androgen Receptor

HISTOLOGICAL TYPES	AR positive	AR negative	Total	P value
Apocrine	3(100%)	-	3	0.61
IDC NOS	18(60%)	12(40%)	30	
Lobular	3(100%)	-	3	
Medullary	-	2(100%)	2	
Metaplastic	2(40%)	3(60%)	5	
Mucinous	3(60%)	2(40%)	5	
Neuroendocrine	1(100%)	-	1	
Papillary	-	1(100%)	1	
Grand Total	30	20	50	

Left sided tumors show 11 cases positive with 57.8% positivity and right sided tumors show 19 cases positive with 61.2% of the cases. But this is not statistically associated. (Table 19 & Chart 14).

Chart-12: AR Expression with Age range

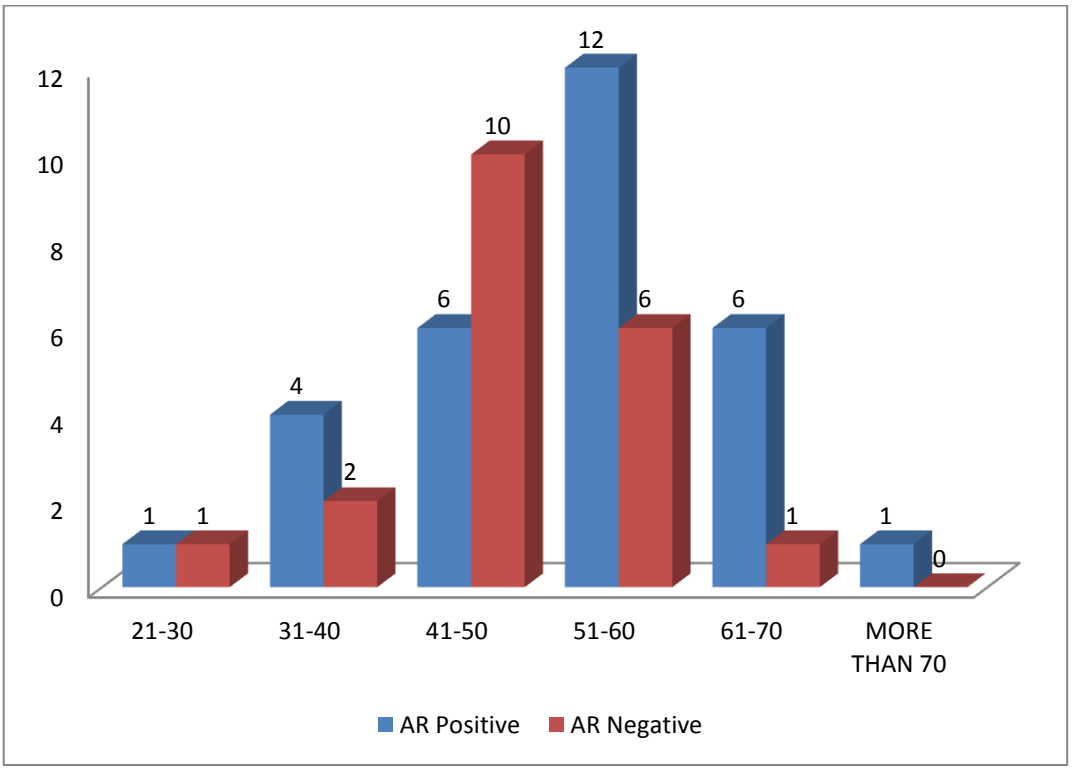


Chart-13: AR Expression with Histological types

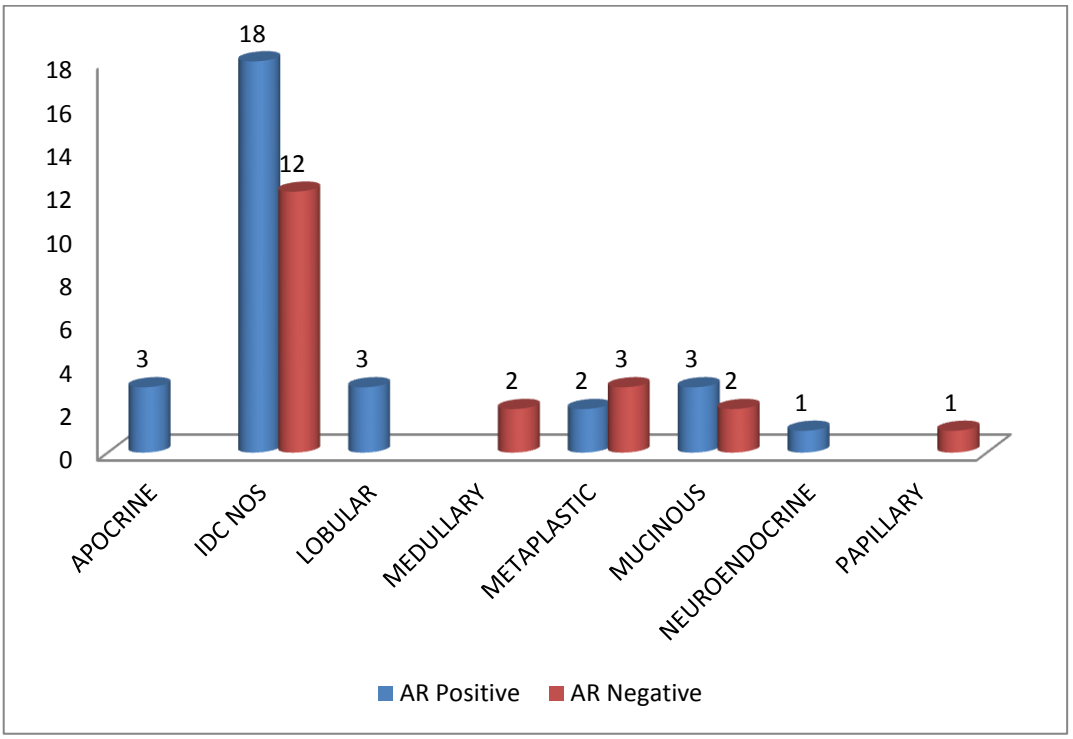
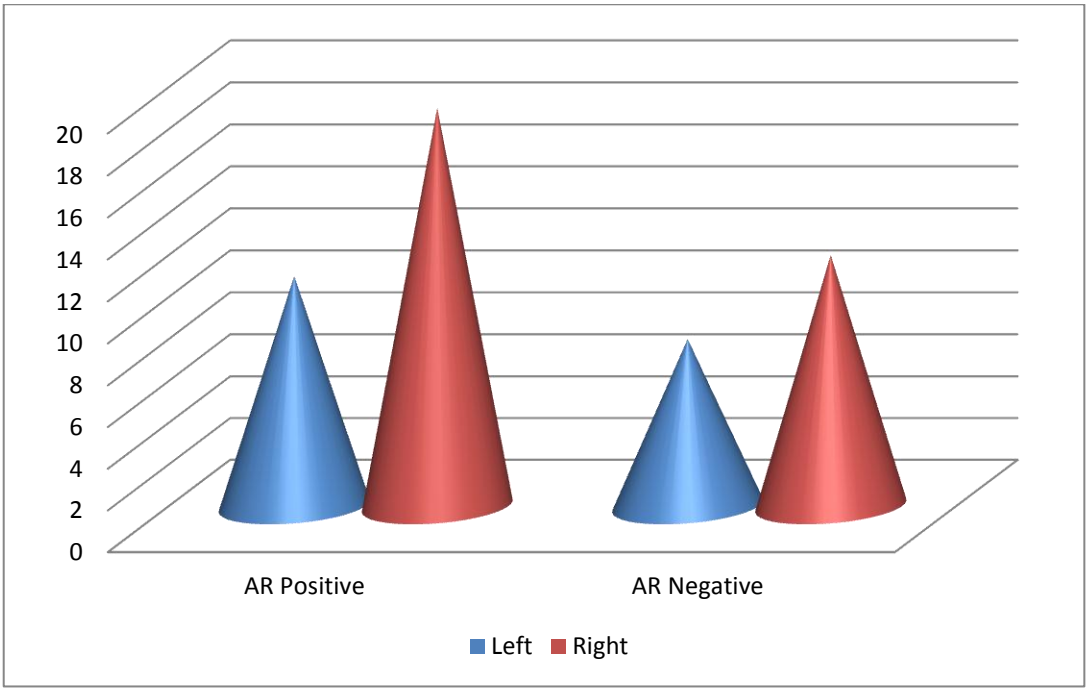


Table-19: Correlation of Side of the cancer with Expression of Andrgen Receptor

Side of the cancer	AR positive	AR negative	Total	P value
Left	11(57.8%)	8(42.2%)	19	0.811964
Right	19(61.2%)	12(38.8%)	31	
Grand Total	30	20	50	

Chart-14: AR with Side of the tumor.



Smaller sized tumors show increased AR expression with T1 tumors showing 100% positivity and large sized tumors show decreased AR expression with T3 showing 36.3% positivity.(Table 20 & Chart 15)

Table-20: Correlation of Tumor size with Expression of Androgen Receptor

SIZE OF TUMOR	POSITIVE	NEGATIVE	TOTAL	P value
<2cm(T1)	2(100%)	0(0%)	2	0.12
2-5cm(T2)	24(64.8%)	13(35.2%)	37	
>5cm(T3)	4(36.3%)	7(63.7%)	11	
TOTAL	30	20	50	

Chart-15: AR with Size of the tumor.

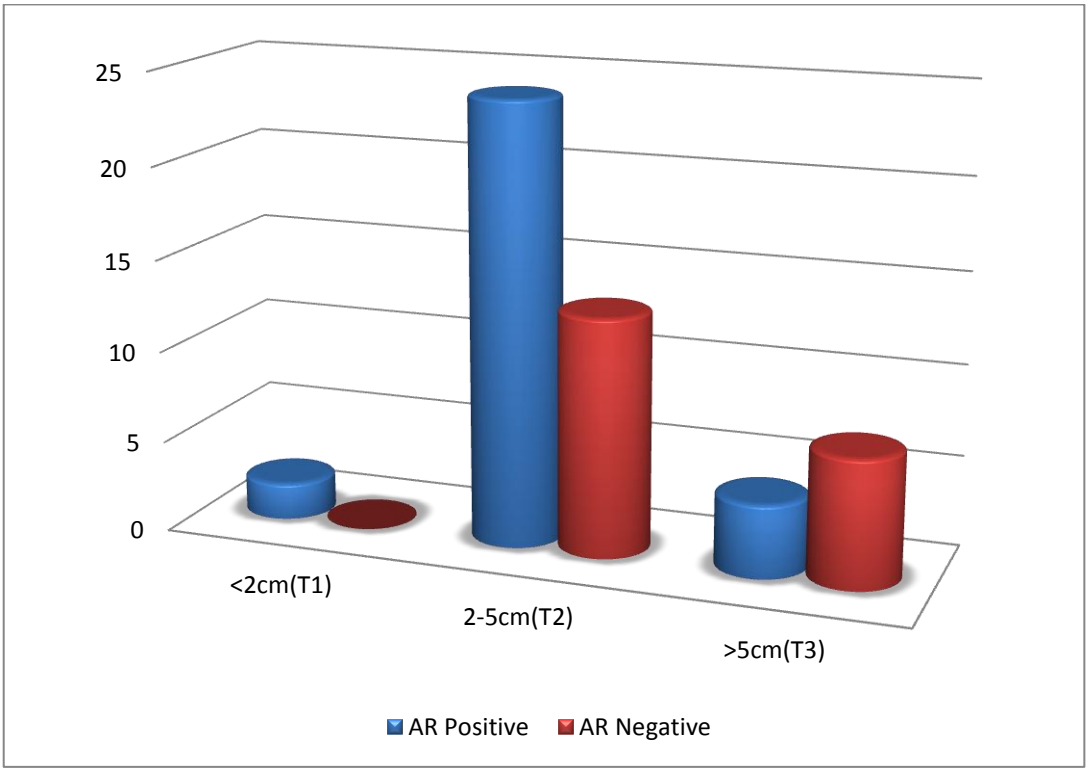


Table-21: Correlation of grade of the tumor with Androgen Receptor.

Grade	AR positive	AR negative	Total	P value
I	6(60%)	4(40%)	10	0.89
II	6(60%)	4(40%)	10	
III	7(70%)	3(30%)	10	
Special types	11(55%)	9(45%)	20	
Total	**30**	**20**	50	

Grade of the tumor is not significantly associated with Androgen Receptor expression in breast cancer with grade III showing 70%. (Table 21 & Chart 16)

Chart-16: AR Expression with grade of the tumor

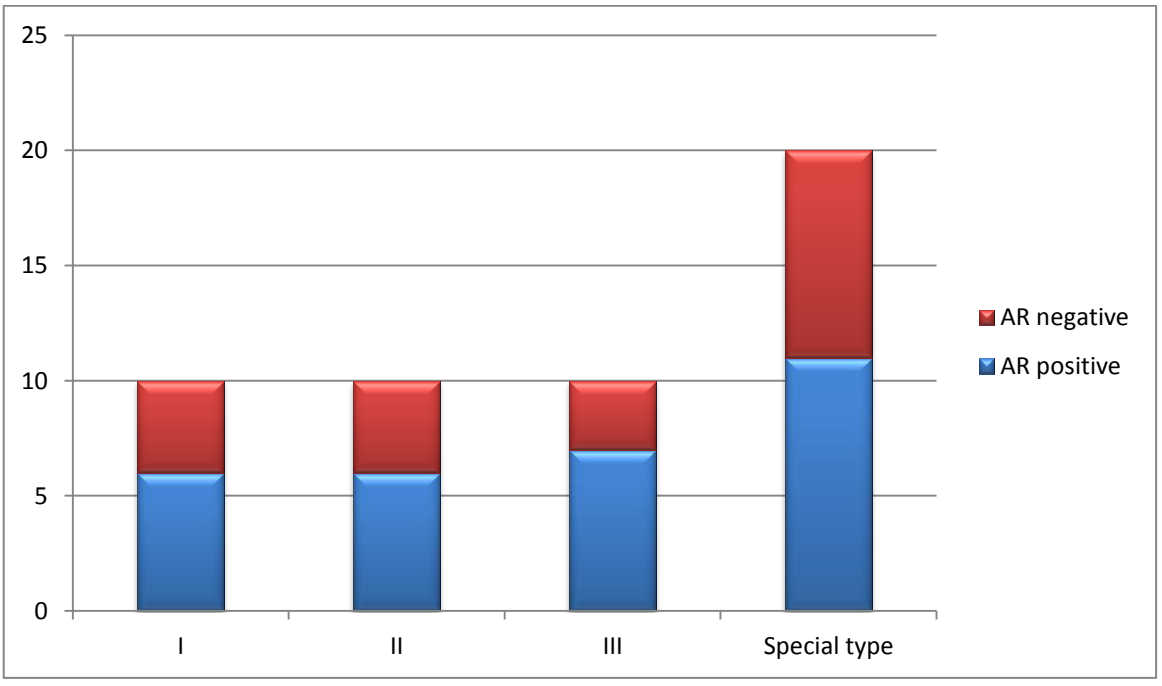
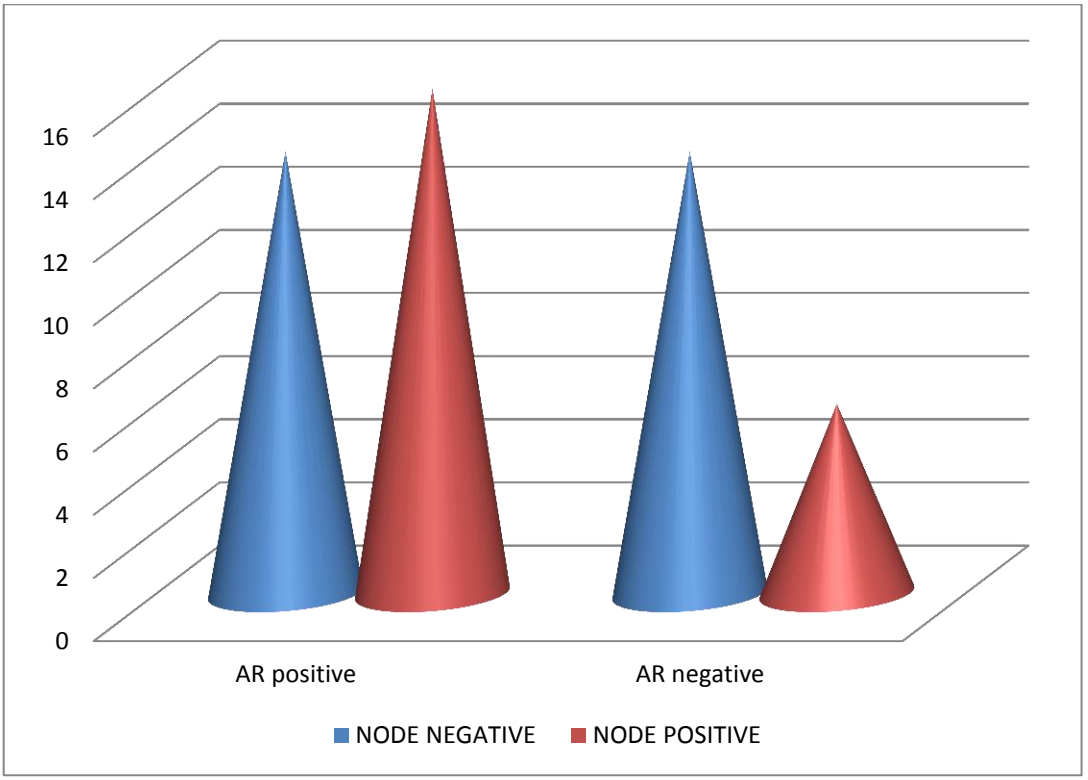


Table-22: Correlation of Lymph node metastasis with Expression of Androgen receptor.

LYMPH NODE STATUS	AR positive	AR negative	Total	P value
NODE NEGATIVE	14(50%)	14(50%)	28	0.1
NODE POSITIVE	16(72.7%)	6(27.3%)	22	
GRAND TOTAL	30	20	50	

Chart-17: AR Expression with Lymph node metastasis.



Androgen Receptor expression is seen more common in node positive tumors with 72.7% of AR positivity seen in node positive tumors.(Table 22, Chart 17)

Table-23: Correlation of Lymphovascular invasion with Expression of Androgen Receptor.

Lymphovascular invasion	AR positive	AR negative	Total	P value
Absent	17(53.1%)	15(46.9%)	32	0.18
Present	13(72.2%)	5(27.8%)	18	
Grand Total	30	20	50	

Tumors with Lymphovascular invasion show increased AR positivity with 72.2% and it is not statistically significant. (Table 23 & Chart 18)

Chart-18: Lymphovascular invasion with AR expression.

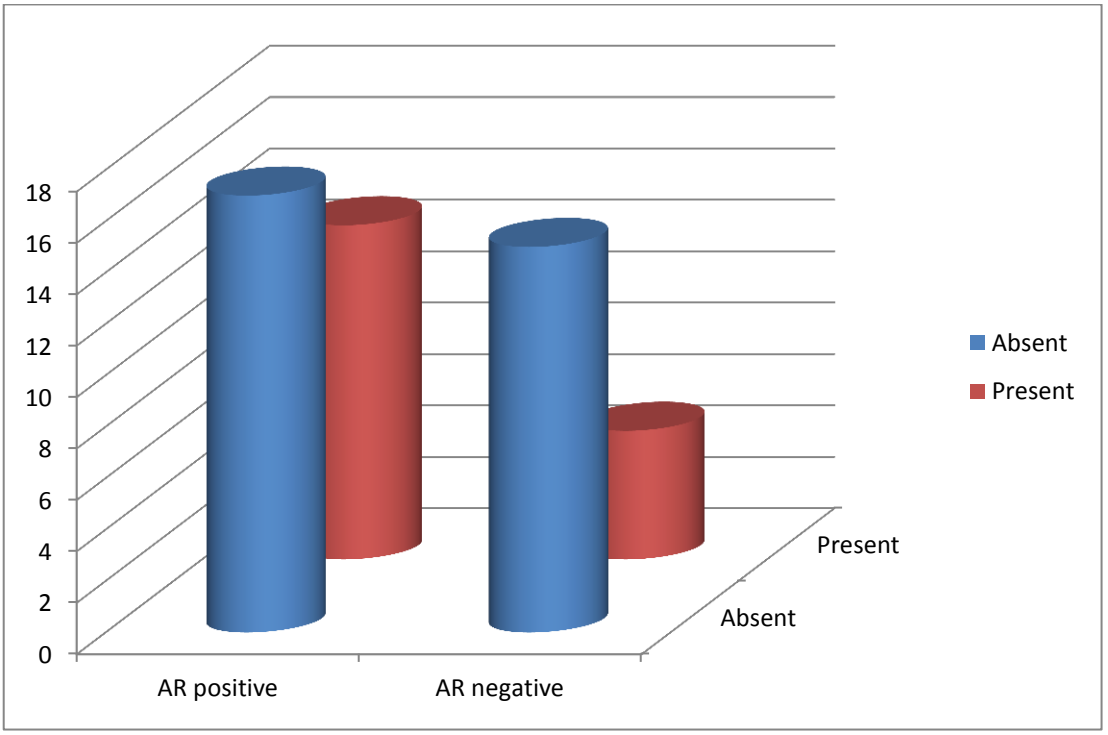


Table-24: Correlation of Lymphocytic infiltration with Expression of Androgen receptor.

Lymphocytic infiltration	AR positive	AR negative	Total	P value
Absent	18(60%)	10(40%)	28	0.485
Present	12(40%)	10(60%)	22	
Grand Total	30	20	50	

AR expression is seen more commonly in tumors presenting with no Lymphocytic infiltration (60%) and it is not significantly associated. (Table 24 & Chart 19)

Chart-19: Lymphocytic infiltration with AR expression.

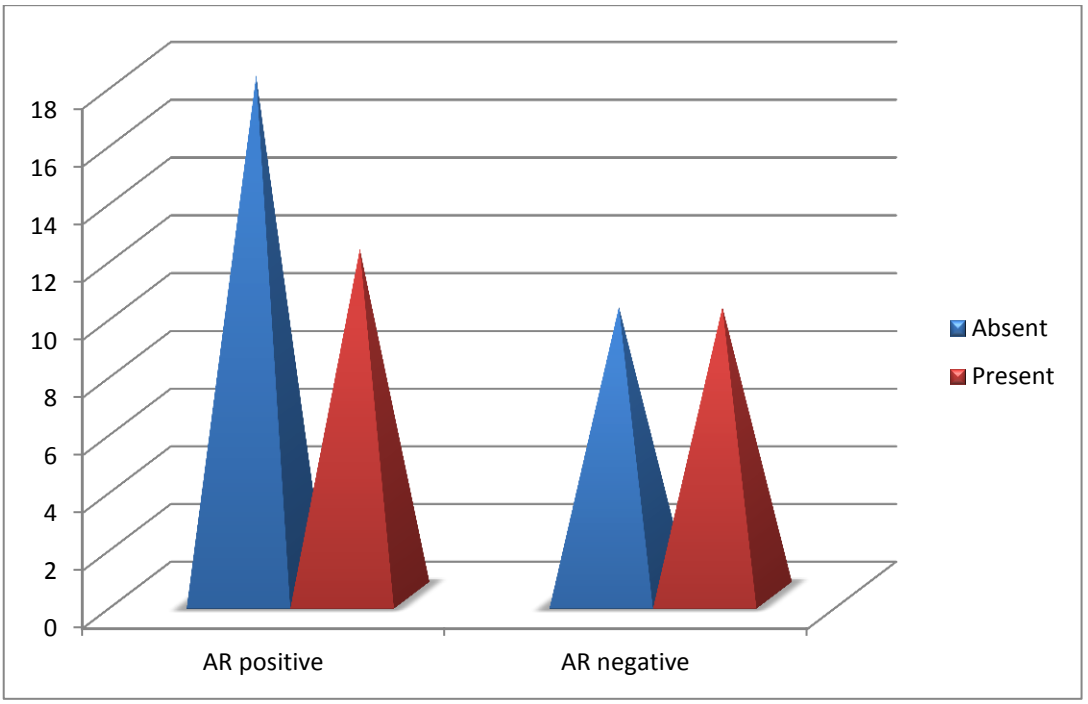


Table-25: Correlation of Tumor necrosis with Expression of Androgen receptors.

Necrosis	AR Positive	AR Negative	Total	P value
Absent	25(59.5%)	17(40.4%)	42	0.874862
Present	5(62.5%)	3(37.5%)	8	
Grand Total	30	20	50	

Tumors with necrosis show more AR positivity (62.5%) than tumors without necrosis (59.5%) though not statistically associated. (Table 25 & Chart 20)

Chart-20: Necrosis with AR expression

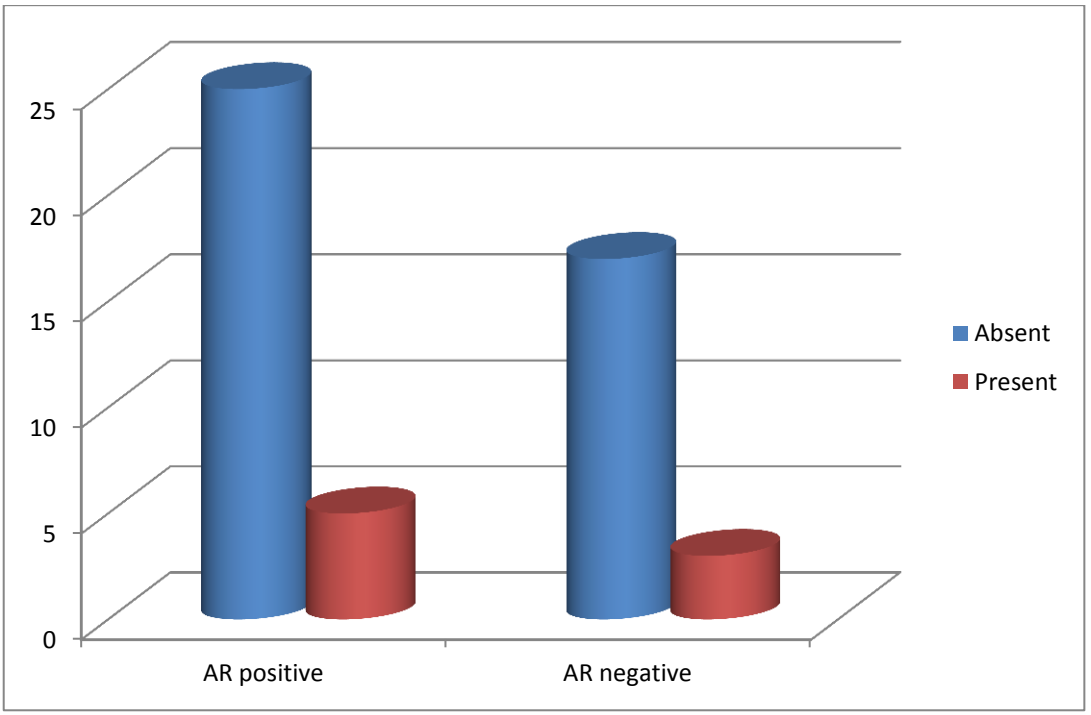


Table-26: Correlation between Skin infiltration with Androgen Receptor

Skin infiltration	AR positive	AR negative	Total	P value
Absent	27(58.6%)	19(41.4%)	46	0.5231
Present	3(75%)	1(25%)	4	
Grand Total	30	20	50	

Presence of Skin infiltration by the tumor is not significantly associated with AR expression though it was found that 75% of tumors with Skin infiltration show AR positivity. (Table 26 & Chart 21)

Chart-21: Skin infiltration with Androgen Receptor.

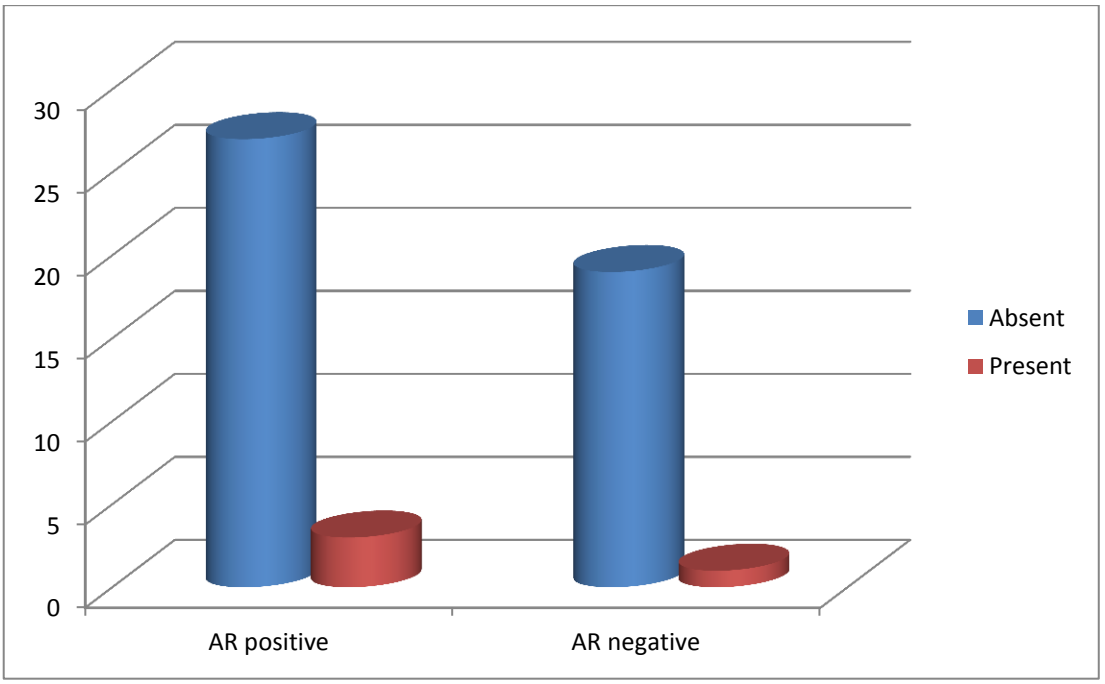


Table-27: Correlation between Estrogen and Androgen receptors

ER expession	AR Positive	AR Negative	Total	P value
ER-neg	10(41.7%)	14(58.3%)	24	0.01101
ER-pos	20(76.9%)	6(23.1%)	26	
Grand Total	30	20	50	

ER positive tumors are more frequently associated with AR expression with 20 out of 26 tumors showing AR positivity constituting 76.9% and it was found that they are statistically significant with p value <0.05. (Table 27 & Chart 22)

Chart-22: Correlation of ER with AR expression.

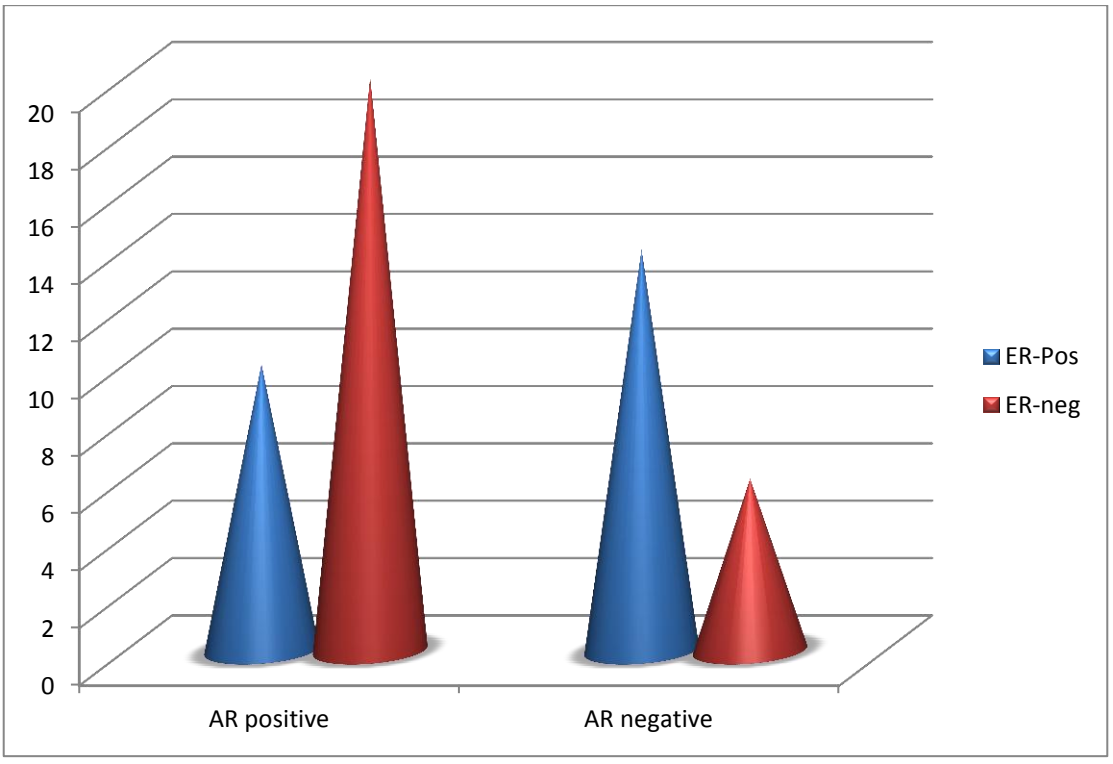


Table-28: Correlation between Progesterone and Androgen receptors.

PR expression	Positive	Negative	Total	P value
PR-neg	11(42.3%)	15(57.7%)	26	0.007862
PR-pos	19(79.1%)	5(20.9%)	24	
Grand Total	30	20	50	

AR expression is significantly associated with Progesterone receptor expression showing 79.1% positivity in PR positive tumors. (Table 28 & Chart 23)

Chart-23: Correlation of PR with AR expression.

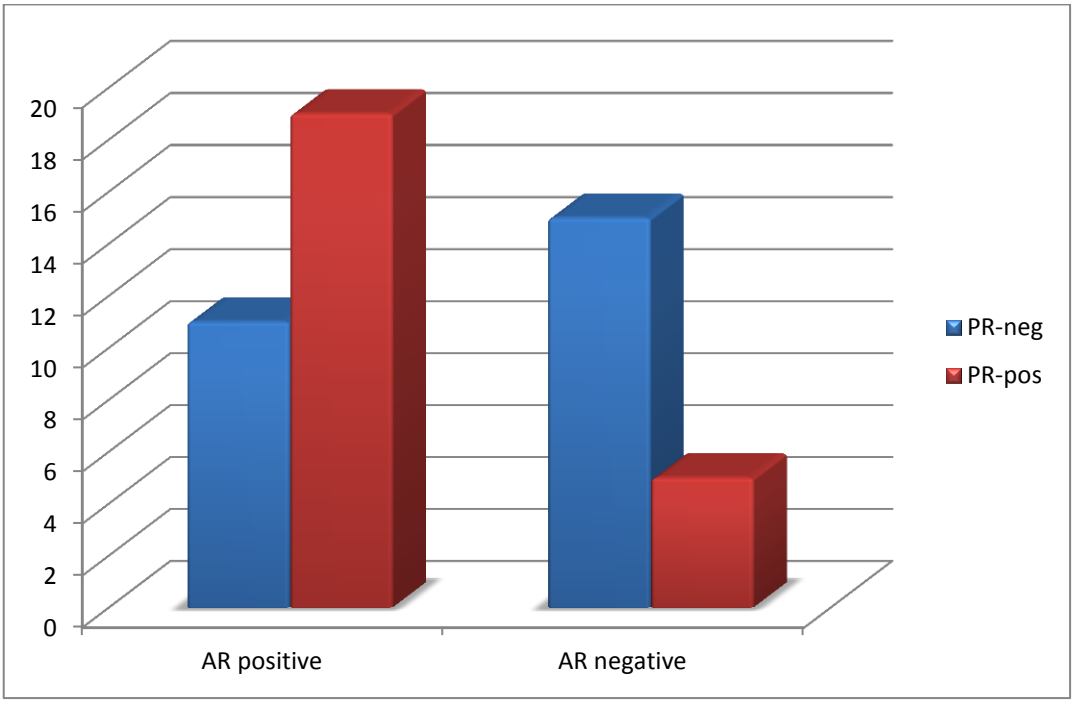


Table-29: Correlation between Expression of HER2neu and Androgen receptor.

HER2neu expression	AR Positive	AR Negative	Total	P value
HER2-neg	21(56.7%)	16(43.3%)	37	0.5886
HER2-pos	9(69.3%)	4(30.7%)	13	
Grand Total	30	20	50	

AR positivity is seen more commonly in cases expressing HER2neu but 56.7% of HER2neu negative tumors also express AR positivity but they are not statistically significant. (Table 29 & Chart 24)

Chart-24: HER2neu expression with AR expression.

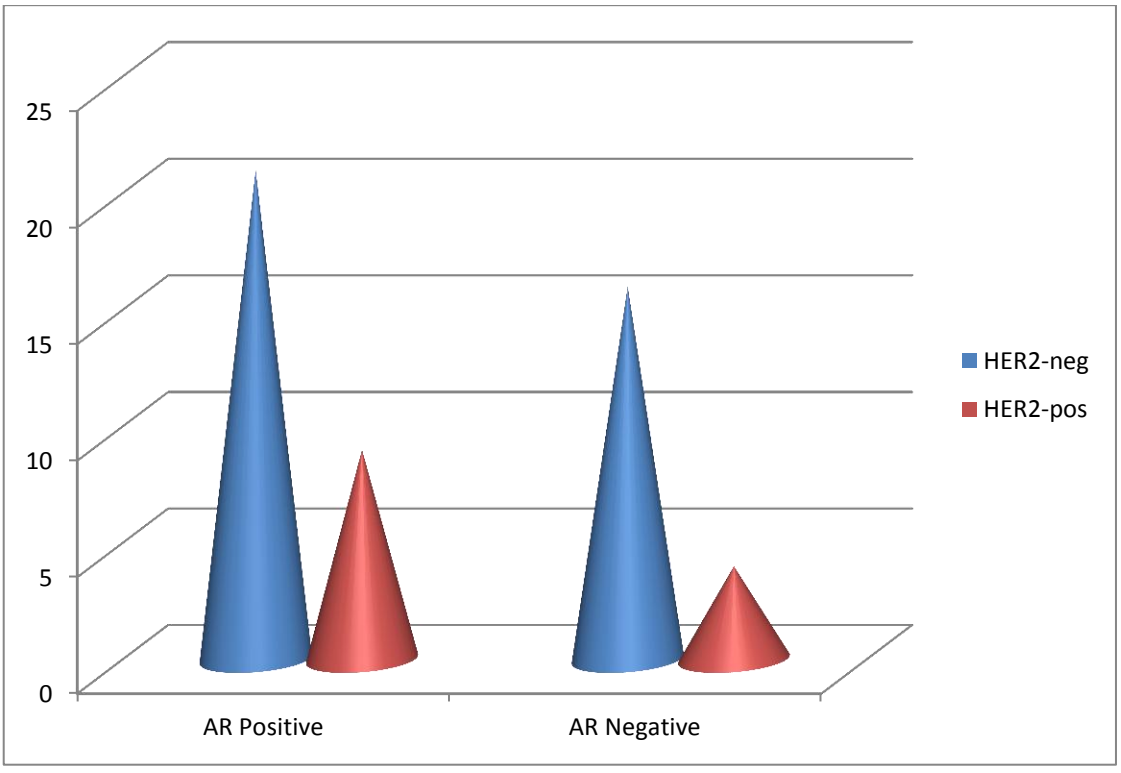


Table-30: Correlation between ER, PR and AR

	AR Positive	AR Negative	Total	P value
ER -,PR -	10(41.6%)	14(58.4%)	24	0.028466
ER+,PR-	1(50%)	1(50%)	2	
ER+,PR+	19(79.1%)	5(20.9%)	24	
ER-,PR+	0(0%)	0(0%)	0	
total	30	20	50	

The tumors which are positive for both ER and PR show maximum positivity for AR with 79.1% and it is statistically significant. (Table 30 & Chart 25)

Chart-25: AR, PR expression with AR expression

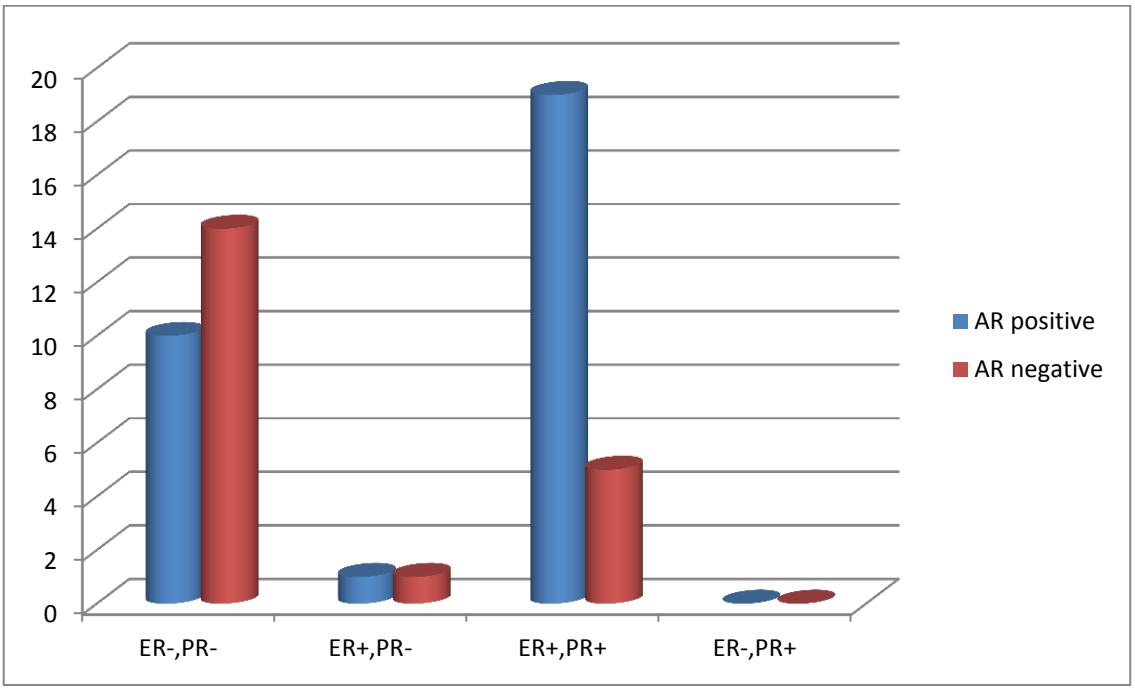
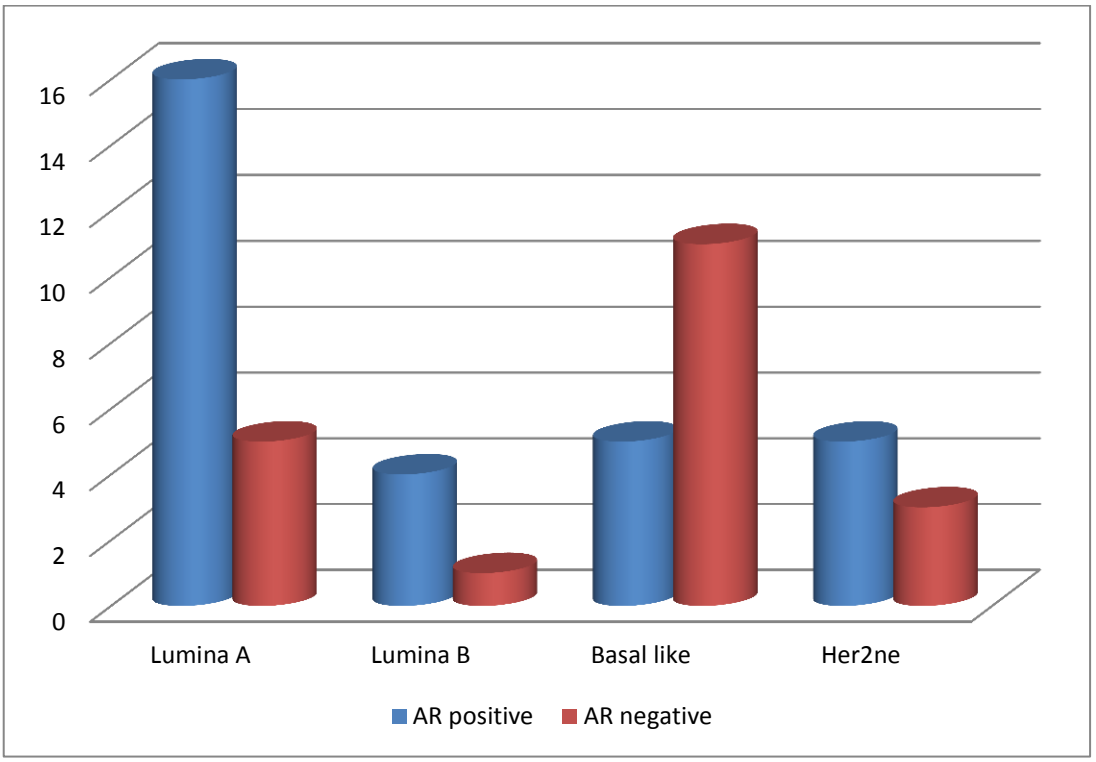


Table-31: Correlation between Molecular classification and Androgen receptor

	Positive	Negative	Total	P value
Lumina A	16(76.1%)	5(23.9%)	21	0.034
Lumina B	4(80%)	1(20%)	5	
Basal like	5(31.25%)	11(68.75%)	16	
HER2neu	5(62.5%)	3(37.5%)	6	
Grand total	30	20	50	

Chart-26: Molecular classification with AR expression



AR expression is significantly associated with Molecular classification showing increased expression in Lumina A and Lumina B subtypes. (Table 31 & Chart 26)

In this study the expression of AR found to be significantly associated with expression of ER, PR and Molecular classification. It is not significantly associated with other clinicopathological factors which can be attributed due to small sample size.

DUCTAL CARCINOMA BREAST

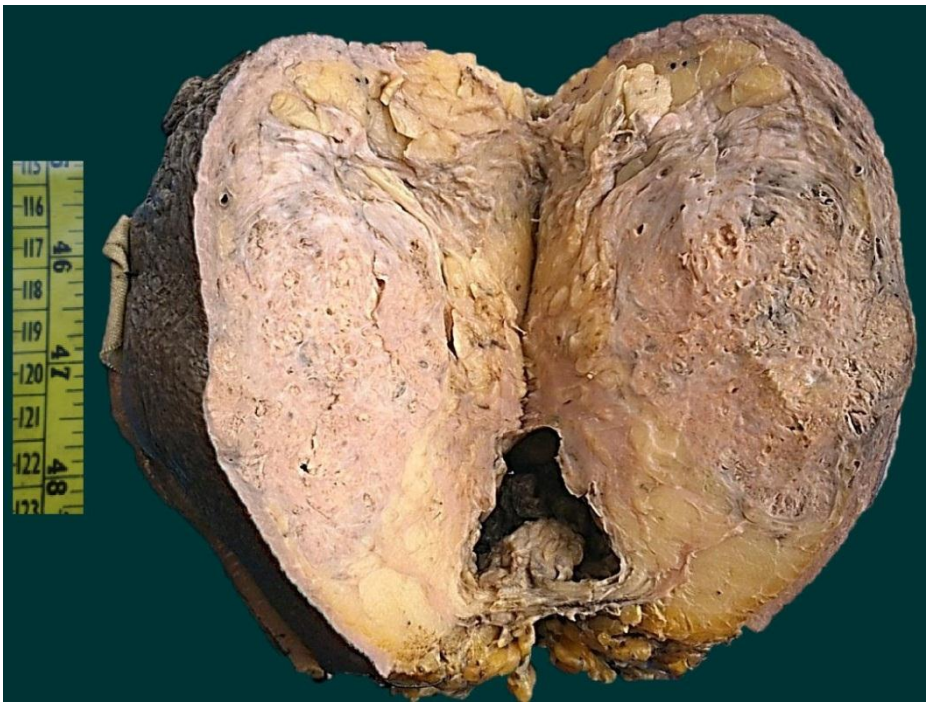


Figure 2: Grey white firm growth with irregular margins

MUCINOUS CARCINOMA

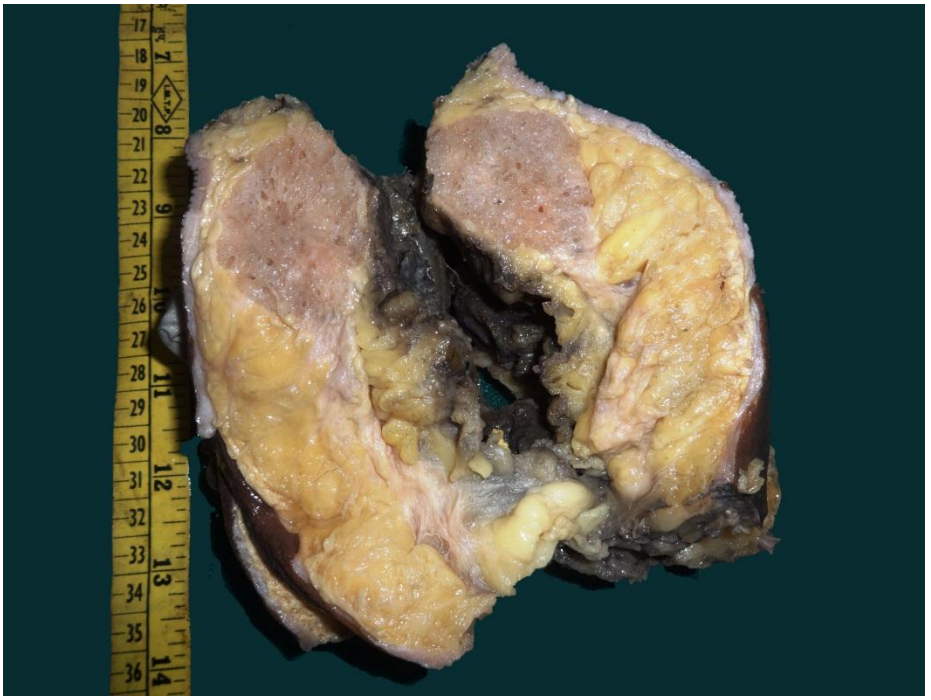


Figure 3: Well circumscribed glistening gelatinous growth

PAPILLARY CARCINOMA

Figure 4: Well circumscribed grey white growth with granular surface

APOCRINE CARCINOMA

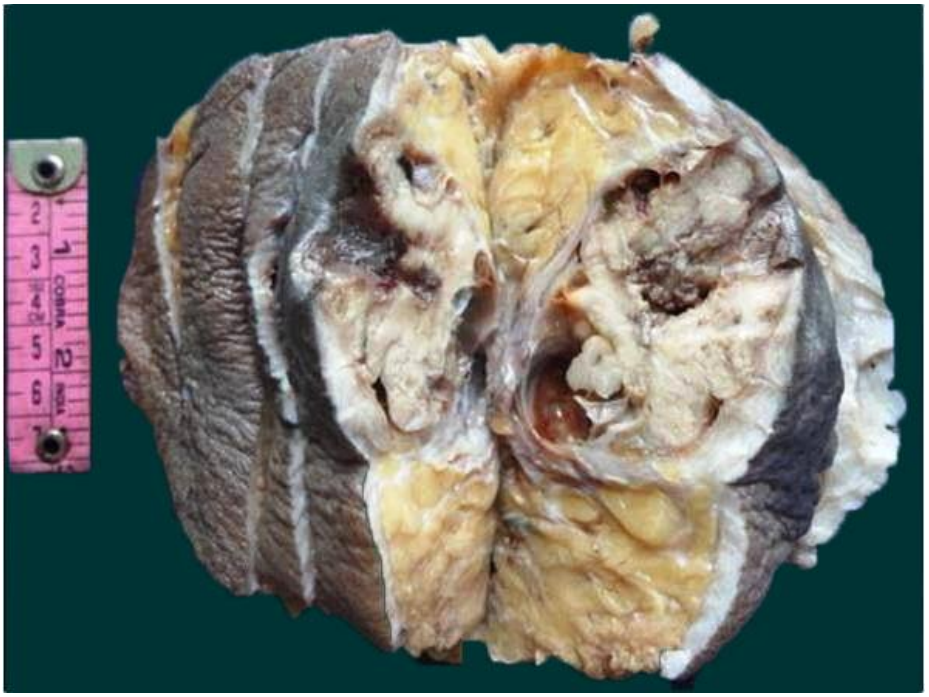


Figure 5: Well circumscribed grey white growth with cystic degeneration and hemorrhage

MEDULLARY CARCINOMA

Figure 6: Well circumscribed greywhite fleshy growth

METAPLASTIC CARCINOMA

Figure 7: well circumscribed grey white firm growth

LOBULAR CARCINOMA

Figure 8: Well circumscribed Gray white

NEUROENDOCRINE CARCINOMA

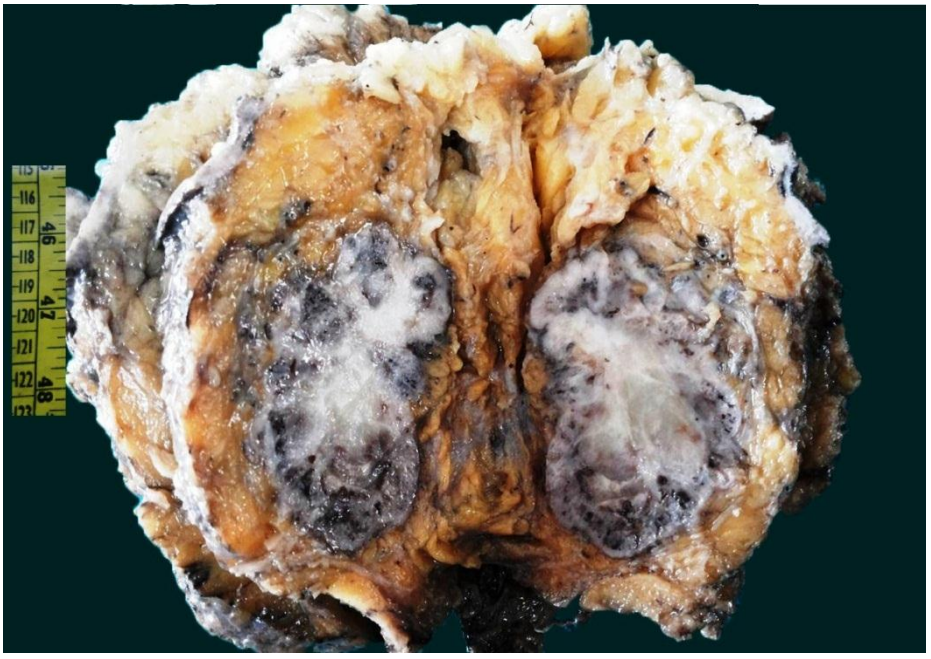


Figure 9 :Well demarcated gray white tumor

INVASIVE DUCTAL CARCINOMA NOS - GRADE 1

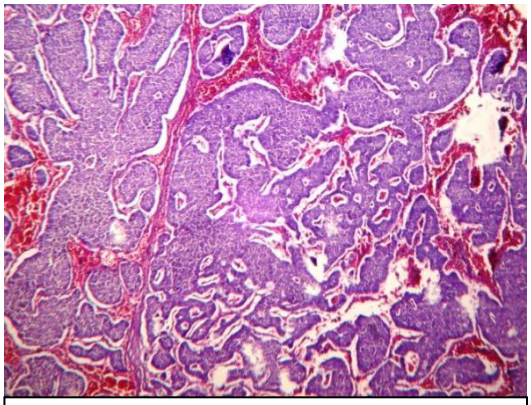


Figure 10: Invasive ductal carcinoma NOS tubule formations >75% tumor cells (40X)

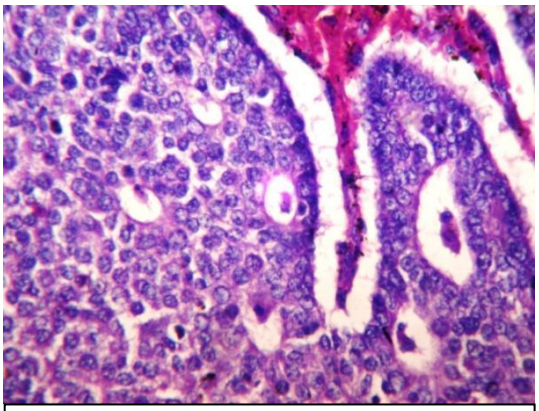


Figure 11: Malignant ductal epithelial cells with mild nuclear pleomorphism & low mitosis (400X)

INVASIVE DUCTAL CARCINOMA NOS GRADE 2

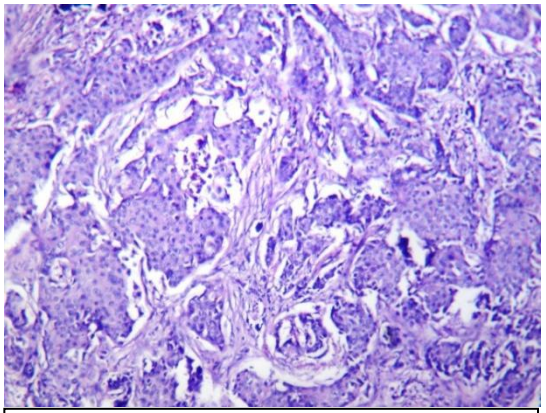


Figure 12: Sheets of malignant ductal epithelial cells, 30% tubule formation (100X)

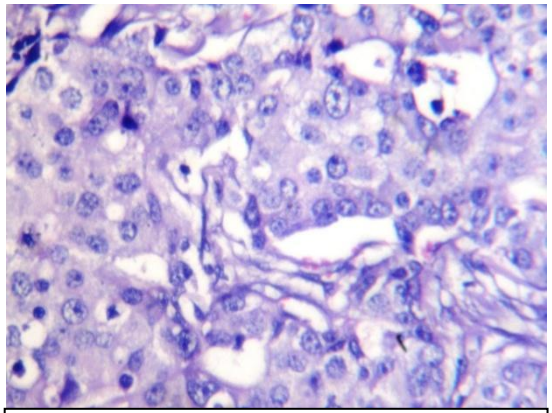


Figure 13: Malignant ductal epithelial cells in sheets, 30% tubules and mild nuclear pleomorphism (400X)

INVASIVE DUCTAL CARCINOMA NOS GRADE 3

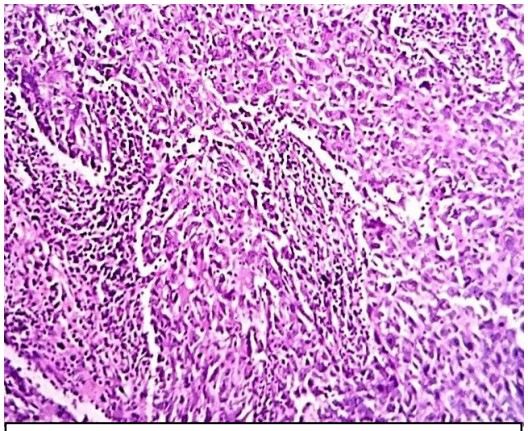


Figure 14: Malignant ductal epithelial cells in sheets (100X)

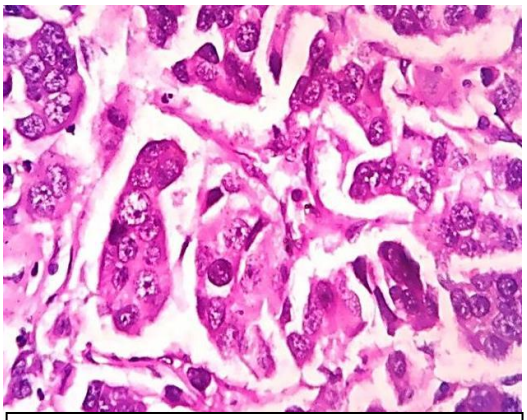


Figure 15: Malignant epithelial cell with marked pleomorphism and increased mitosis.(400x)

MUCINOUS CARCINOMA

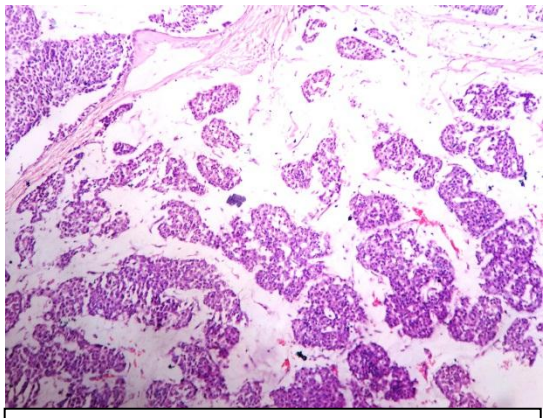


Figure 16: Tumor nests floating in mucin (100X)

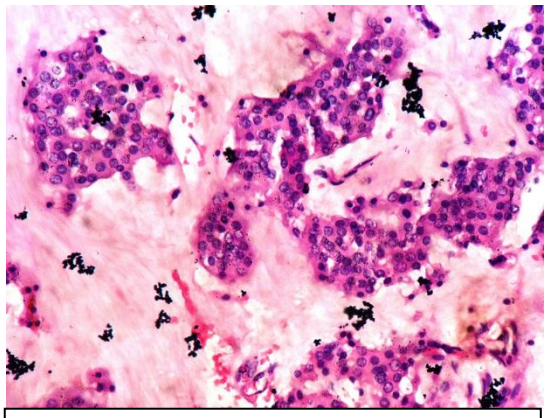


Figure 17: Malignant ductal epithelial cells with mild nuclear pleomorphism and no mitosis (400X)

LOBULAR CARCINOMA

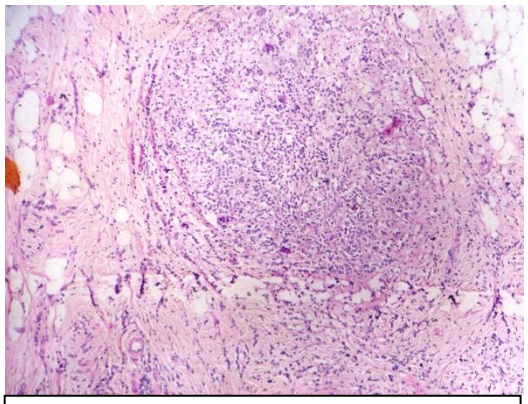


Figure 18: Tumor cells arranged in lobular pattern with pagetoid spread around ductal elements(100X)

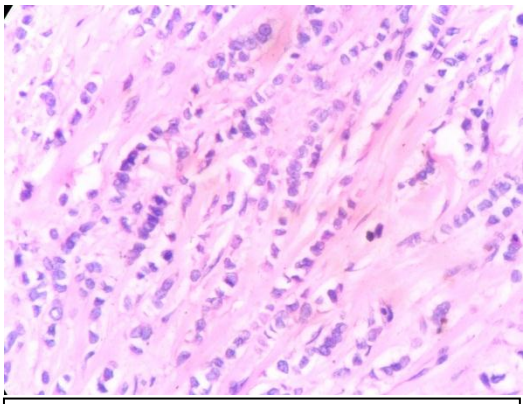


Figure 19: Tumor cells arranged in singles in Indian file pattern (400X)

MEDULLARY CARCINOMA

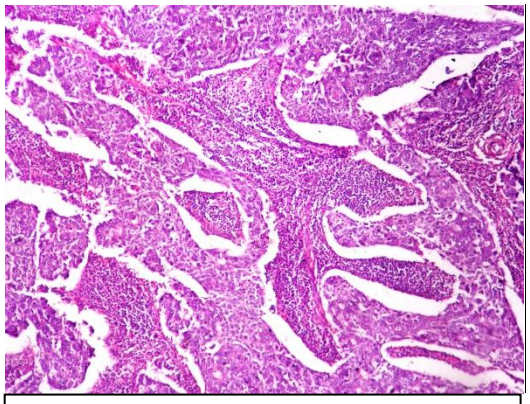


Figure 20: nodular arrangement of tumor cells with lymphoplasmacytic infiltrate in periphery (100X)

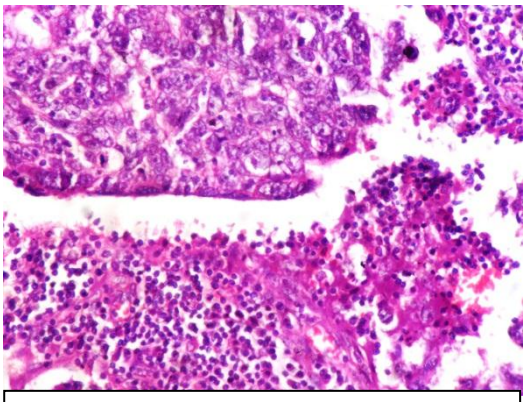


Figure 21: tumor cells in syncytial pattern with marked nuclear pleomorphism and prominent nucleoli (400X)

PAPILLARY CARCINOMA

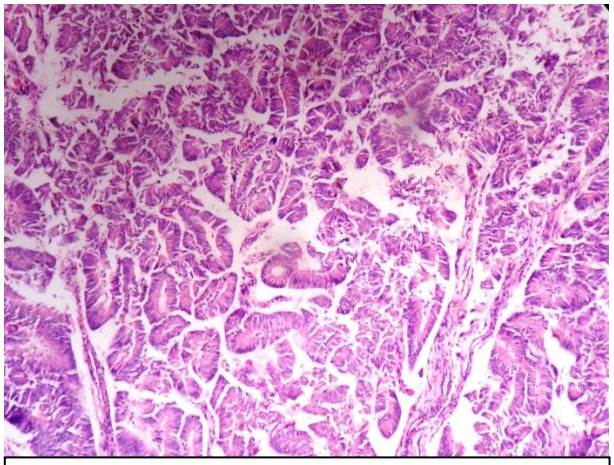


Figure 22: Tumor cells in papillary pattern (100X)

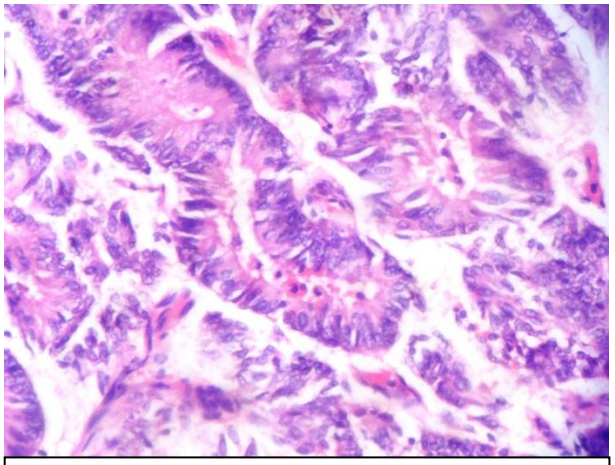


Figure 23: Tumor cells in delicate papillary pattern (400X)

APOCRINE CARCINOMA

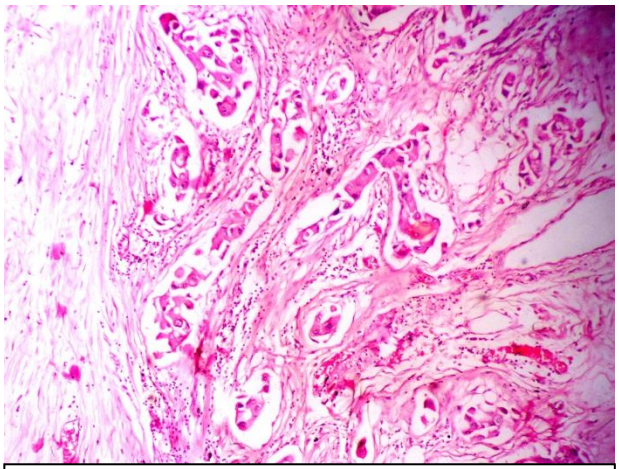


Figure 24: Apocrine cells in papillary pattern (100X)

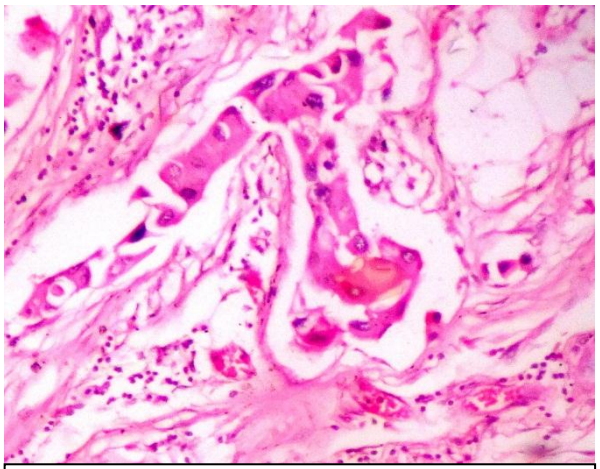


Figure 25: Apocrine cells with abundant granular eosinophilic cytoplasm (400X)

METAPLASTIC CARCINOMA WITH SPINDLE DIFFERENTIATION

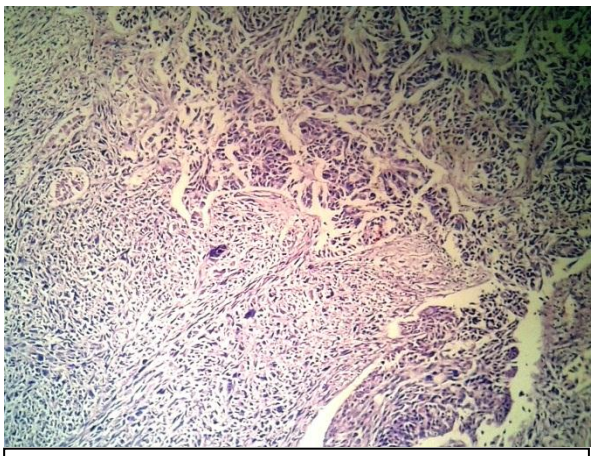


Figure 26 : Malignant epithelial cells with spindle cell differentiation (100x)

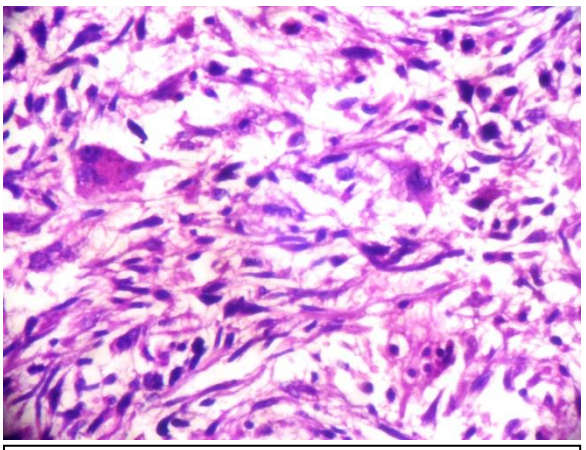


Figure 27: Malignant spindle cells with multinucleated giant cell (400x)

NEUROENDOCRINE CARCINOMA

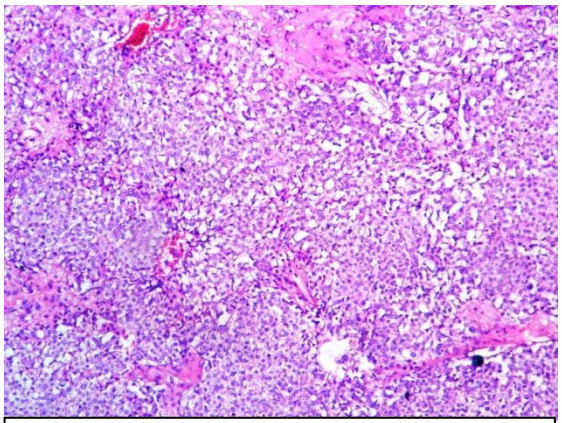


Figure 28: tumor cells in nests separated by fibrovascular septa (100x)

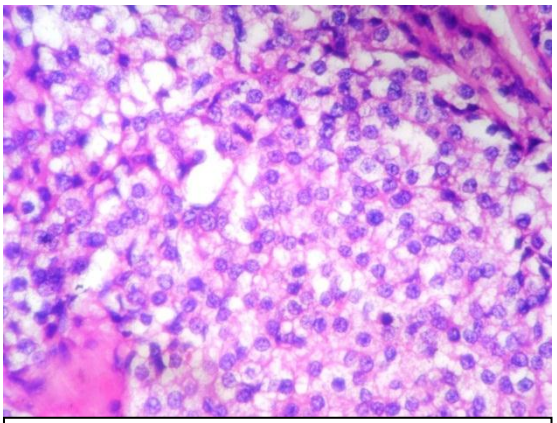


Figure 29: uniform oval shaped tumor cells with salt and pepper chromatin (400x)

OTHER PROGNOSTIC FACTORS

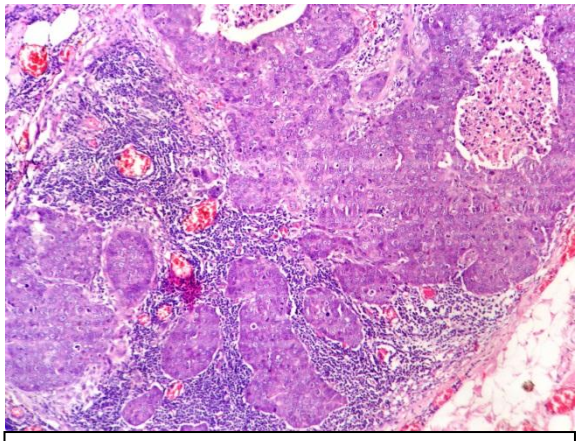


Figure 30:Metastatic deposit in node

(100X)

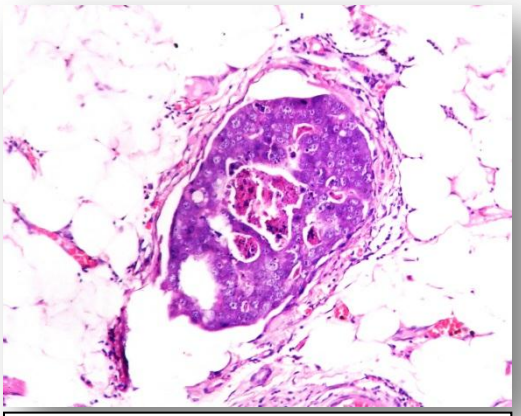


Figure 31: Lymphovascular invasion (100x)

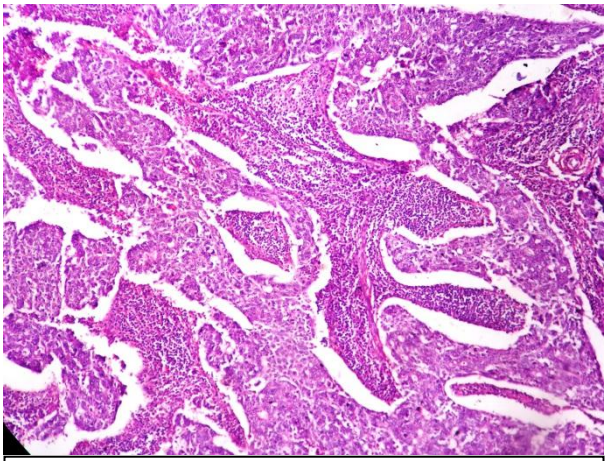


Figure 32 : Lymphocytic infiltration (100X)

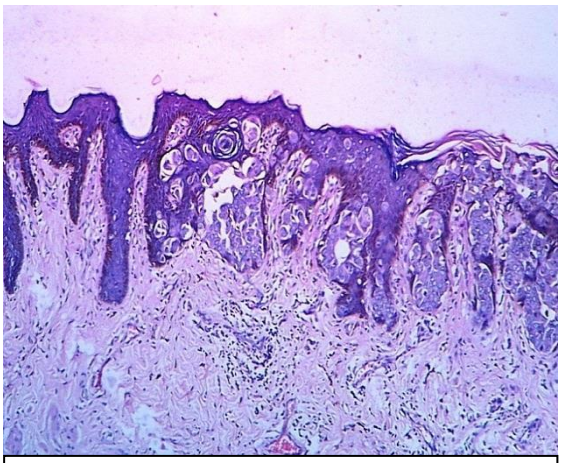


Figure 33: Skin infiltration (100X)

ESTROGEN RECEPTOR EXPRESSION

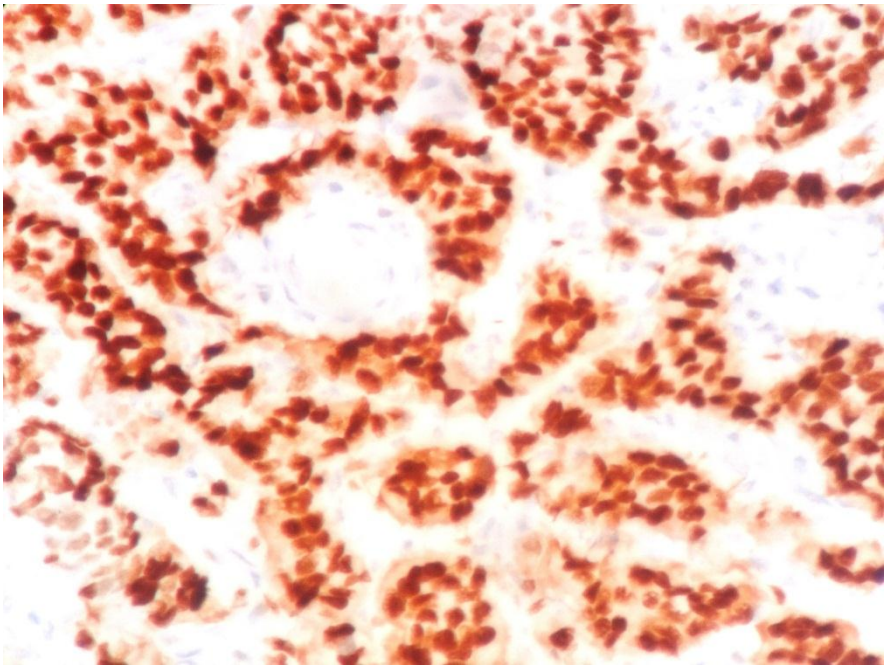


Figure 34: Invasive Ductal Carinoma NST. Positive nuclear staining (5+3) for ER

PROGESTERONE RECEPTOR EXPRESSION

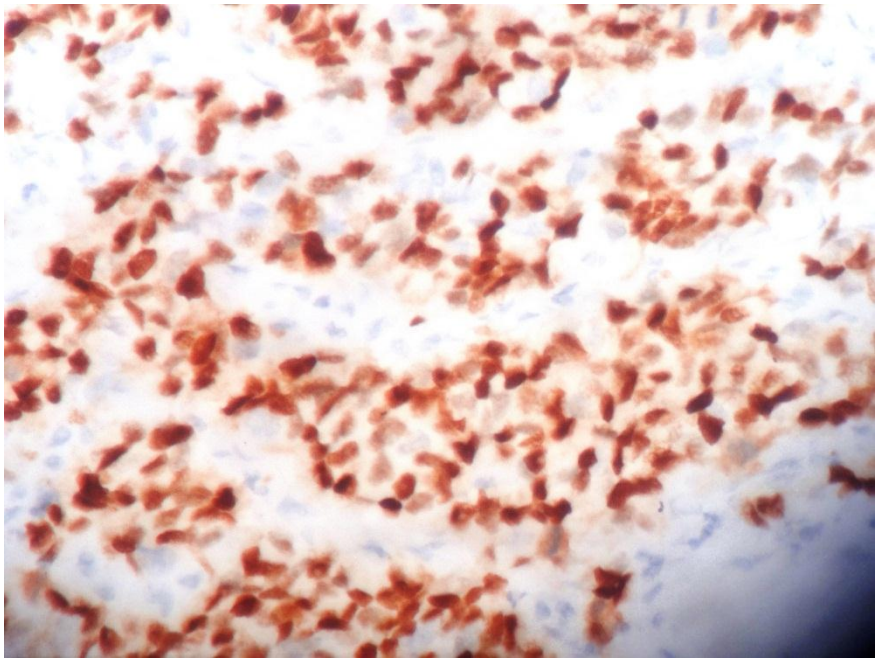


Figure 35: Invasive Ductal Carcinoma NST. Positive nuclear staining (5+3) for PR

HER2neu EXPRESSION

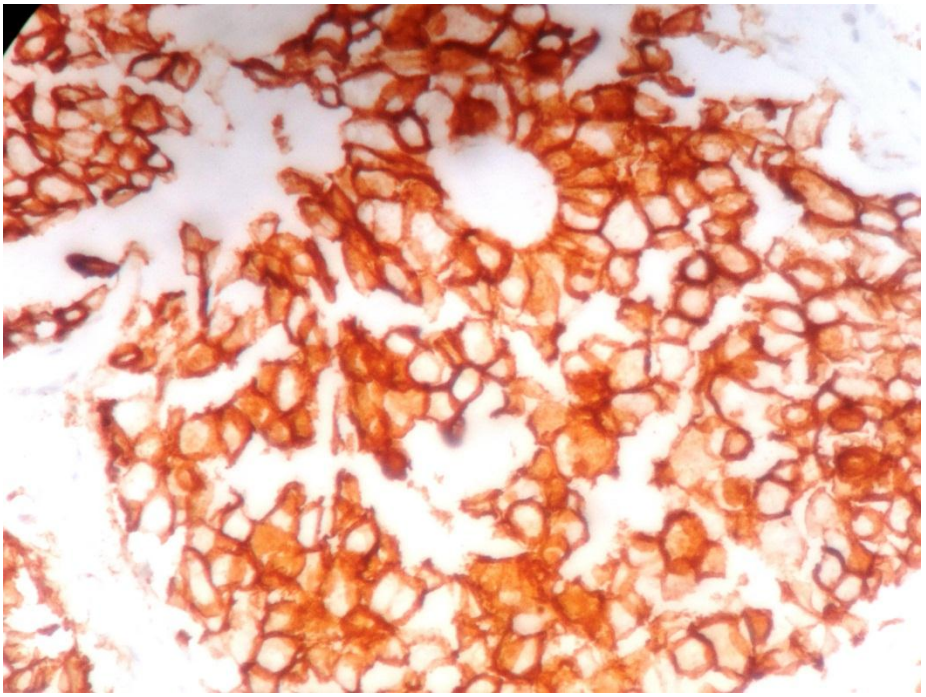


Figure 36: Invasive Ductal Carcinoma NST. Cytoplasmic positivity (3+) of HER2neu

ANDROGEN RECEPTOR EXPRESSION

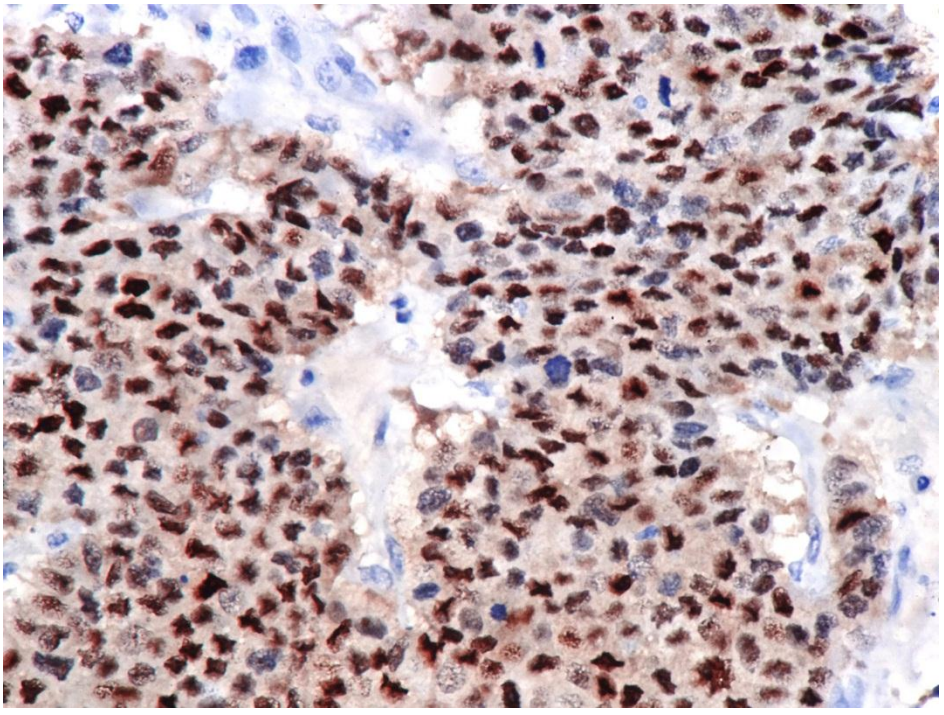


Figure 37: Invasive Ductal Carcinoma NST. Positive nuclear staining (5+3) for Adrogen receptor.

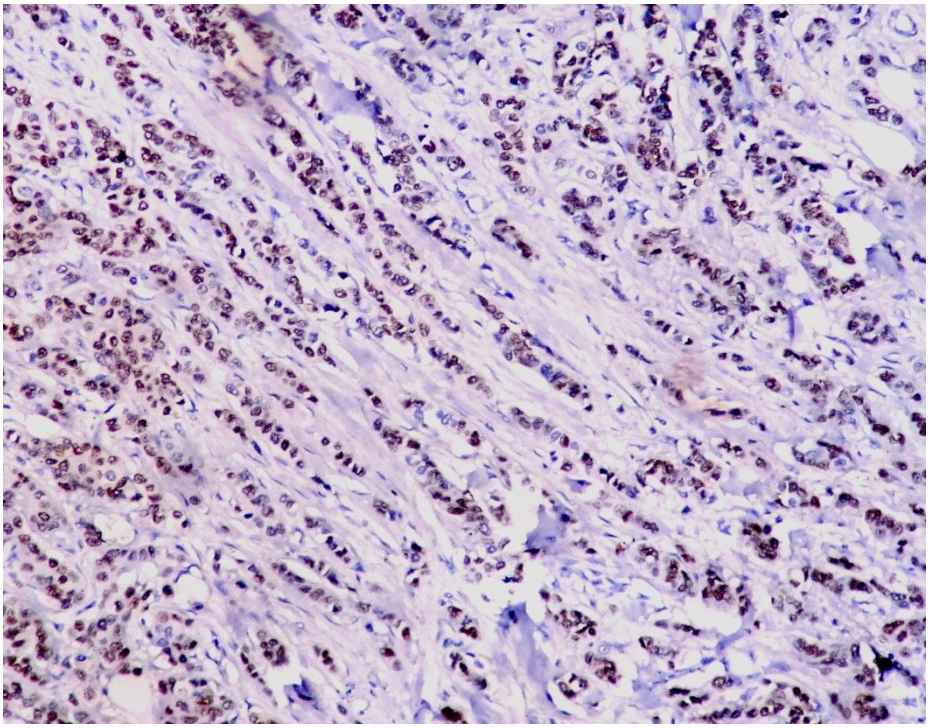


Figure 38: Lobular Carcinoma of Breast. Positive nuclear staining (5+3) for Androgen Receptor

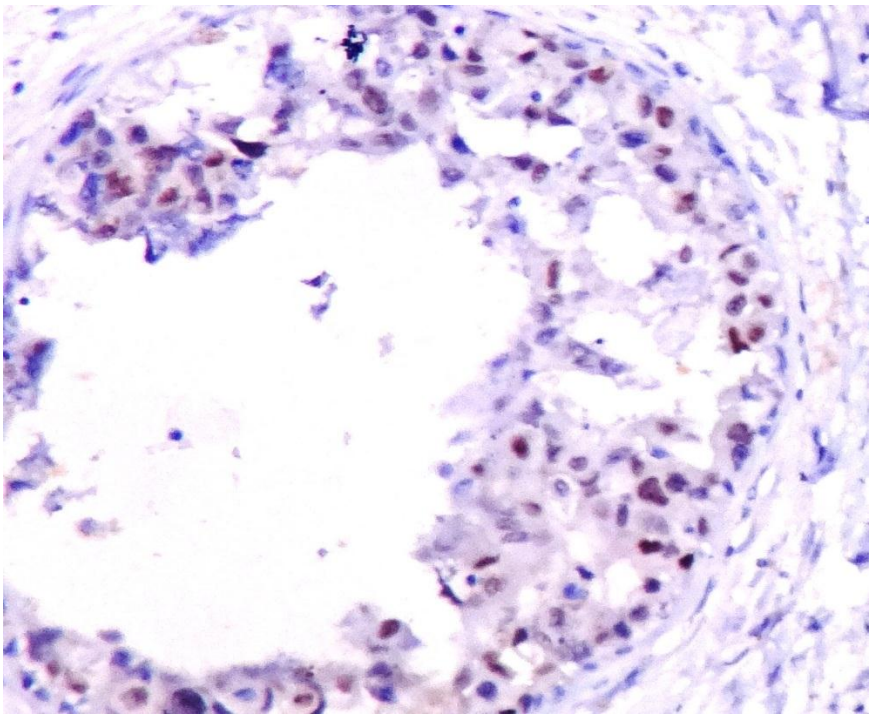


Figure 39: Apocrine Carcinoma of breast. Positive nuclear staining (5+2) for Androgen receptor.

DISCUSSION

DISCUSSION

Among the urban population breast carcinoma comprise the most common cause for cancer related mortality and it is the second most common cause in rural women. [131] It is a heterogeneous disease with varying clinical and pathological presentation.

Hence we can reduce the mortality of breast cancer by early detection, appropriate management and targeted therapies. Many theories underlie the pathogenesis of breast cancer and there are many prognostic factors. Apart from the prognostic markers like stage, grade, Lymph node status, ER, PR and HER2neu, many newer markers are under study. One such attempt was made to detect Expression of Androgen receptor.

In this present study, Immunohistochemistry was done in 50 cases and the expression was correlated with the clinicopathological factors.

Madras Medical College being a tertiary care center, among the surgical specimens received Breast tumors constitute 4.15% of all cases. Malignant breast tumors constitute 43.63% of all the breast specimens received.

The youngest age presented with breast cancer is 30 years and older age group reported to be 75 years with 52.5 as median age of presentation. This compared with study by Micello et al, [132] Carreno et al, [133] Hu et al, [134] Honma et al [135] showed that in Indian population there is

a shift in breast cancer presentation towards younger age group in the recent years. (Table 32) The highest incidence of breast cancer reported in 41 to 50 year age group. This is in concurrence with the study done by Rajesh Singh Laishramet al. [136]

Table-32: Comparison of Median age

	Median age of presentation
Micello et al.2010 [132]	58.7
Carreno et al.2007 [133]	61
Hu et al.2011 [134]	61
Honma et al.2012 [135]	56
Current study	52.5

Among the histological types Invasive ductal carcinoma NOS type comprise the most common with 89.62%. This coincides with the study of Albrektsenet al, [137] Shirley SE et al [138] and AM Daudaet al. [139] The incidence of invasive ductal carcinoma NOS type is higher in Indian population (89.62%) compared to that of western population accounting for the worse prognosis (Table 33)

Majority of the breast cancers are seen in T2 category which is similar to the study by lakmini et al. But comparing with the study by Christine L [140] Carter et al the proportion of T2 in Indian population(70.28%) is higher than in Western population(55.4%). (Table 34)

Table 33: Comparison of distribution of histological subtypes of breast cancers

Histological subtypes	AM Dauda et al [139]	Shirley SE et al [138]	Albrektsen et al [137]	Current study
Invasive ductal carcinoma	78.8%	69.3%	81.4%	89.62%
Lobular carcinoma	6.7%	5.6%	6.3 %	1.42%
Tubulolobular carcinoma	-	0.5%	-	-
Mixed carcinoma	-	-	-	-
Mucinous carcinoma	2.4%	3.6%	2%	2.36%
Micropapillary carcinoma	-	0.5%	-	-
Microinvasive	-	0.3%	-	-
Papillary carcinoma	4.2%	3.5%	-	0.47%
Metaplastic carcinoma	2.4%	1.3	-	2.83%
Tubular carcinoma	-	0.8%	2%	-
Cribriform carcinoma	-	0.1%	-	-
Medullary carcinoma	3.6%	1%	1.1%	0.94%
Apocrine carcinoma	-	-	-	1.89%
Adenoid cystic carcinoma	-	0.1%	-	-
Malignant phyllodes	1.8%	-	0.4%	-
Neuroendocrine	-	-	-	0.47%
Inflammatory carcinoma	-	1.4%	-	-
Other specific types	-	-	1.2%	-
Adenocarinomas unspecific	-	5.3%	5.5%	-

Table-34: Comparison of size of tumors (%)

Size	Christine L. Carter et al [140]	F S Al-Joudi et al [141]	Lakmini et al [142]	Current study
T1	33.6	3.14	14.5	4.25%
T2	55.4	19.37	74	70.28%
T3	11	77.49	11.5	25.47%

The Grade II tumors were more frequent than other grades of breast cancers. This observation is in concordance with the study carried out by Qiu Jet al [143] , Carey et al [144] and GG Van den Eynden et al [145] (Table 35).

Table 35: Comparison of grade of tumor (%)

Grade	Qiu J et al [143]	Carey et al [144]	GG Van den Eynden et al [145]	Current study
Grade I	33.3	25	32.63	20.00%
Grade II	54	26	36.84	62.11%
Grade III	12.7	49	30.53	17.89%

60.85 % of the cases showed lymph node metastasis and 37.26% cases with 1-3 nodes positive. This results coincides with the study done by Jun Qiu et al [143] and SE Shirley et al [138] who reported nodal metastasis in 60.32% and 75.7% of their cases.

There were lymphocytic infiltration in 53.3%, skin infiltration in 8.02% and necrosis in 32.5% of the cases, in concurrence to the 33% skin infiltration reported in the study conducted by Chanda Bewtra et al [146] and 38.1% necrosis in the study conducted by Gloria Perio et al. [147]

Table-36: Comparison of molecular classification

	Adedayo et al [148]	Current study
Lumina A	68.9	41.50943
Lumina B	10.2	12.73585
HER2neu positive	7.5	14.15094
Triple negative	13.4	31.60377

Our study shows Maximum number of cases in Lumina A category constituting 41.5% of cases which is in concurrence with the study by Adedayo et al who shows maximum (68.9%) cases in Lumina A. (Table 36)

COMPARISON OF AR EXPRESSION WITH OTHER SUDIES

In this study AR was expressed in 60% of breast cancers which coincides with studies by Agoff et al [128], Park et al. [126] (Table 37)

Table-37: Comparison of AR Expression

	AR positivity %
Park et al [126]	58
Yu et al [129]	72
Hu et al [134]	79
Peters et al [149]	54
Agoff et al [128]	58
Agrawal et al [117]	43
Current study	60

The present study shows expression of AR more in the age group of 51-60 years constituting 40% of all AR positive cases. But this is not statistically significant. This result coincides with study by park et al [126] which shows increased AR expression in age group over 35 years.

The current study shows increased expression of AR in Apocrine, Lobular and Neuroendocrine carcinoma and it is not statistically significant. But the study by Park et al [126] in which Loular carcinoma shows 83%

positivity and Leo A Neimeier et al [125] which shows AR positivity in 58.3% cases of Apocrine differentiation. (Table 38)

Table-38: Comparison of AR Expression among Histological types

	AR positive % of respective category		
	Park et al [126]	Mishra e al [130]	Current study
IDC NOS	73.68	40.5	60
Lobular	83.3	37.5	100
Mucinous	41.7		60
Medullary	25		0
Tubular	100		-
Papillary	81.8		0
Metaplastic	50		40
Apocrine			100
Neuroendocrine			100

Park et al [126] shows that AR positivity in more in T1 stage (62.1%) and established a significant association. The present study also shows increased AR expression in T1 stage (100%) but it was not significantly associated.

70% of grade III tumors are AR positive, 60% of grade II and 60% of grade I tumors are AR Positive but there is no significant association between them. Park et al [126] established a significant association between grade II

tumors and AR. Mishra et al [130] established a significant association between Lower grade tumors and AR.

In our study AR positivity is more common in Node positive cases constituting 72.72% cases and this result coincides with study by Park et al [126] who showed 69.2%. The study by Mishra et al [130] showed Maximum AR positivity in node negative tumors but none of the studies is statistically significant.

The current study shows that there is an inverse correlation between Lymphovascular invasion, Lymphocytic infiltration, Skin invasion, Presence of necrosis and Androgen receptor though it is not statistically significant.

Correlation of AR with Hormonal Receptors.

In our study AR positivity is higher in cases which are ER positive constituting 76.9% of ER positive cases. This correlation is statistically significant. This result is in concordance with other studies.

76.9% cases of ER positive are AR positive and they are significantly associated. The comparison with other studies is given in table 39.

Yu et al [129] studied 564 cases and found 74.9% of HER2neu negative tumors are AR positive. Similar study done by Park et al [126] with 413 cases shows 70.7% of HER2neu negative tumors are AR positive. Our study also shows similar results with 56.75% of HER2neu negative tumors with AR positivity though it was not statistically significant. A functional crosstalk

between AR and HER2neu signaling pathway has been shown in in vitro studies and gene expression profiling in ER negative tumors by Naderi et al [150] and Doane et al [113]

Table-39: Comparison of ER Expression with AR Expression

	ER positive % among AR positive tumors.	PR positive % among AR positive tumors.
Park et al [126]	83.3	82.0
Leo A Niemeier et al [125]	94.7	-
A.K.Agrawal et al [117]	43.7	60
Yu et al [129]	88.8	78.2
Current study	76.9	79.16

Table-40: Comparison of % of ER, PR positive tumors that are AR positive.

	A.K.Agrawal et al [117]	Agoff et al [128]	Current study
ER +,PR +	57	100	79.1
ER +,PR -	34.4	67	50
ER -,PR +	63.6	0	0
ER -,PR -	60.3	50	4.16

The present study shows 79.1% of both ER and PR positive tumors are AR positive and this result is statistically significant. Similar results also obtained in studies by A.K.Agrawal et al [117] and Agoff et al. [128] (Table 40)

Table-41: Comparison of AR expression in Molecular classification

	Yu et al [129]	Leo A Niemeier et al [125]	Current study
Lumina A	83.5	96	76.2
Lumina B	75.6	86	80
Triple negative	39	10	31.25
HER2neu positive	55.8	63	62.5

80% of Luminal A tumors are AR positive and 76.2% of Luminal B tumors are AR positive and this study shows a significant association between them. (Table 41)

This study shows significant expression of Androgen receptor (60%) in Primary breast cancer especially in ER and PR positive tumors.

LIMITATIONS OF THE STUDY

- The cases were selected on the basis of histopathological classification in the tertiary care Centre and not a population base study, which will not reflect the true prevalence of the general population

- HER2neu expression has an intermediate stain scoring of 2+ which requires FISH for grading it as negative or positive.
- Gene expression profiling will give more accurate expression of AR and molecular subtypes than immunohistochemistry, but being expensive it cannot be applied to all patients.
- Follow up details of the cases has not been available and Targeted therapies has not been done which helps to assess the prognostic and theranostic significance of Androgen receptor.

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SUMMARY

SUMMARY

This is the study conducted in Institute of Pathology, Madras Medical College, Chennai during the period between Jan 2013 to June 2015. It is a Prospective and retrospective study. Out of the 27576 specimens received during this period, 1515 cases were breast specimens. Of these 1145 were breast tumors constituting for 4.15% of all cases.

Non neoplastic cases were 370 and 484, 661 cases (including incisional and excisional biopsies) were benign and malignant breast tumors respectively, thus constituting 24.42% non-neoplastic cases, 31.95% benign cases and 43.63% malignant cases.

Of the total 364 Mastectomy specimens, detailed history regarding Patient's age, sex, side of the breast involved, Grade, Lymph node involvement, Lymphocytic infiltration, Necrosis, Skin infiltration by tumor and Hormonal status like status of ER, PR, HER2neu were assessed for 212 cases. For AR estimation 50 cases were randomly selected including 30 Infiltrating Ductal carcinoma-NOS cases and 20 cases of special types like Mucinous, Medullary, Metaplastic, Apocrine, Papillary, Lobular and Neuroendocrine carcinoma.

Immunohistochemistic analysis of AR was done in these cases. Slides were evaluated and scoring was done by Alred scoring system and results were compared with other Histopathological parameters and Hormonal receptors like ER, PR and HER2neu status.

- Highest incidence of breast carcinoma occur in the age group of 41-50 years.
- Infiltrating Ductal Carcinoma is the most common primary malignant neoplasm of breast constituting 89.6% of cases.
- Most of the malignant tumors are Right sided.
- 70.3% of cancers are presented in the size range of 2-5cms.
- Majority of the tumors are of Grade II accounting for 62.1% of all cases.
- 60.9% cases presented with Lymph node metastasis and majority of them with N1 stage.
- Lymphovascular invasion was seen in 46.7% of cases and Lymphocytic infiltration seen in 53.3% cases.
- Necrosis was present in 32.6% of cases
- Skin infiltration was observed in 8% of cases
- Estrogen receptor expression was observed in 51.42% cases and Progesteron receptor was observed in 46.7% cases.
- 26.89% of cases were positive for HER2neu.
- As per Molecular classification, Lumina A constitute maximum number of cases with 41.5% and Lumina B constitute 12% cases. HER2neu alone positive in 14.15% case and Triple negative in 31.6% cases.
- Androgen receptor expression was seen in 60% of cases.
- More number of cases are AR positive in the age group of more than 60 years though it was not statistically significant
- AR expression is seen in 100% cases of Apocrine carcinoma, Lobular carcinoma and Neuroendocrine carcinoma. Although this result was limited

by small sample size, many studies shows similar results. AR expression was minimal or absent in Medullary carcinoma, Metaplastic carcinoma and Papillary carcinoma.

- Smaller size tumors show maximum positivity with 100% positivity observed in T1 cancers and this result is in concordance with many studies.
- There is no association obtained between Grade and AR expression in this study though many studies show significant association with low grade tumors.
- Many lymph node positive tumors are AR positive but not significantly associated.
- Androgen receptor expression is more in cases with Lymphovascular invasion and cases without Lymphocytic infiltration.
- Breast cancers with necrosis and skin involvement show increased AR expression.
- ER positive tumors are significantly associated with AR expression than ER negative tumors. 41% of ER negative tumors also express AR.
- AR expression is significantly more in PR positive tumors.
- 56% of HER2neu negative tumors are AR positive and 69.2% of HER2neu positive tumors are AR positive.
- 63.3% of total cases are Positve for all three markers-ER, PR, AR. And 41% of ER-/PR- tumors are AR positive.
- AR expression is seen maximum in Luminal A and Luminal B subtypes of tumors.

- 31.25% of Triple negative tumors(ER-/PR-/HER2neu-) are AR positive explaining the implication of AR related targeted therapy in these tumors.
- In this present study AR is significantly associated with ER and PR positive tumors and Luminal A and Luminal B subtypes of Molecular classification.

CONCLUSION

CONCLUSION

In this study, the incidence of IDC-NOS type forms the highest among primary breast cancers. Luminal A subtype constitute majority of cases followed by Luminal B subtype.

AR is expressed in 60% of cases of Primary breast carcinoma.

The expression of AR is significantly associated with ER and PR expression and seen more in Luminal A and Luminal B subtype which have better prognosis and hence it could be an independent prognostic factor.

Even though the study was done only in a small number of cases AR is frequently expressed in Apocrine carcinoma, Lobular carcinoma and Neuroendocrine carcinoma.

Although impact of AR in the outcome of breast cancer has not been established, its expression is tend to be seen in tumors of smaller size, Lymph node involvement. There is no association established between AR expression and grade.

AR is significantly expressed in some proportion of Triple negative breast cancer which implicate the use of Androgen related targeted therapy in these cases.

In conclusion, AR is expressed in significant number of breast cancers and expression parallels ER and PR expression. It could be an independent prognostic marker and additional AR related targeted therapies can be done.

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ANNEXURES

ANNEXURE – I

PROFORMA

Case number : Name :

HPE numbe : Age :

IP number : Sex :

Clinical diagnosis :

Menstrual status :

Risk factors if any :

Side of breast : Right/Left

Specimen : Simple Mastectomy / Modified radical mastectomy / Radical Mastectomy / Toilet mastectomy / Others

GROSS

Specimen size :

Nipple areola and Skin :

Tumor size : Tumor margin :

Appearance :

Resected margins : Superior : Inferior :

Medial : Lateral :

Posterior :

Associated findings :

Total number of nodes dissected :

Largest node size :

MICROSCOPY

Histological subtype :

Histological score : Nuclear score: Mitotic score:

Modified Scarf Bloom Richardson Grade: I / II / III

Skin : Free / Involved

Nipple & Areola : Free / Involved

Margins : Superior : Free / Involved Inferior : Free / Involved

Medial : Free / Involved Lateral : Free / Involved

Posterior : Free / Involved

Lymphatic invasion : Present / Absent

Vascular invasion : Present / Absent

Lymphocytic infiltration : P resent / Absent

Necrosis : P resent / Absent

Associated breast lesions :

Total number of nodes dissected :

Number of nodes involved :

ANNEXURE II

WHO HISTOLOGICAL CLASSIFICATION OF EPITHELIAL BREAST TUMORS

INVASIVE BREAST CANCERS

Invasive ductal carcinoma not otherwise specified
Mixed type carcinoma
Pleomorphic carcinoma
Carcinoma with osteoclastic type of giant cells
Carcinoma with choriocarcinomatous features
Carcinoma with melanotic features
Invasive lobular carcinoma
Tubular carcinoma
Invasive cribriform carcinoma
Medullary carcinoma
Mucinous carcinoma
Cystadenocarcinoma
Signet ring carcinoma
Neuroendocrine tumors
Solid neuroendocrine carcinoma
Atypical carcinoid tumor
Small cell/oat cell carcinoma
Large cell neuroendocrine carcinoma
Invasive papillary carcinoma
Invasive micropapillary carcinoma
Metaplastic carcinoma
Apocrine carcinoma
Pure epithelial metaplastic carcinoma
Squamous cell carcinoma
Adenocarcinoma with spindle cell metaplasia
Adenosquamous carcinoma
Mucoepidermoid carcinoma
Mixed epithelial/mesenchymal metaplastic carcinoma
Lipid rich carcinoma
Secretory carcinoma
Oncocytic carcinoma
Adenoid cystic carcinoma
Acinic cell carcinoma
Glycogen rich carcinoma
Sebaceous carcinoma
Inflammatory carcinoma
Intraductal papillary carcinoma
Intracystic papillary carcinoma
Microinvasive carcinoma

NON INVASIVE BREAST CANCERS

Ductal carcinoma in situ
Lobular carcinoma in situ
Atypical papilloma

BENIGN EPITHELIAL TUMORS

Tubular adenoma
Lactating adenoma
Apocrine adenoma
Pleomorphic adenoma
Ductal adenoma
Papilloma

FIBROEPITHELIAL TUMORS

Fibroadenoma
Phyllodes tumor
Benign
Borderline
Malignant
Periductal stromal sarcoma
Mammaryhamartoma

INTRADUCTAL PROLIFERATIVE LESIONS

Atypical ductal hyperplasia
Flat epithelial atypia
Usual epithelial hyperplasia

METASTATIC TUMORS

ANNEXURE III

NOTTINGHAM MODIFICATION OF SCARF BLOOM

RICHARDSON GRADING SYSTEM

TUBULE FORMATION	**SCORE**
Tubule formation in >75% of the tumor	1
Tubule formation in 10 to 75% of the tumor	2
Tubule formation in <10 % of the tumor	3

NUCLEAR PLEOMORPHISM	**SCORE**
Minimal variation in size and shape of nuclei	1
Moderate variation in size and shape of nuclei	2
Marked variation in size and shape of the nuclei	3

MITOTIC RATE	**SCORE**
<10 Mitosis per 10 high power field	1
10 to 20 mitosis per 10 high power field	2
>20 mitosis per 10 high power field	3

GRADE	***SCORE***
Grade 1:	3, 4, 5
Grade 2:	6, 7
Grade 3:	8, 9

ANNEXURE IV

IMMUNOHISTOCHEMISTRY PROCEDURE

1. 4µ thick sections were cut from formalin fixed paraffin embedded tissue samples and transferred to gelatin-chrome alum coated slides.
2. The slides were incubated at 58ºC for overnight.
3. The sections were deparaffinized in xylene for 15 minutes x 2 changes.
4. The sections were dehydrated with absolute alcohol for 5 minutes x 2 changes.
5. The sections were washed in tap water for 10 minutes.
6. The slides were then immersed in distilled water for 5 minutes.
7. Heat induced antigen retrieval was done with microwave oven in appropriate temperature with appropriate buffer for 20 to 25 minutes.
8. The slides were then cooled to room temperature and washed in running tap water for 5 minutes.
9. The slides were then rinsed in distilled water for 5 minutes.
10. Wash with appropriate wash buffer (phosphate buffer) for 5 minutes x 2 changes.
11. Apply peroxidase block over the sections for 10 minutes.
12. Wash the slides in phosphate buffer for 5 minutes x 2 changes.
13. Cover the sections with power block for 15 minutes.
14. The sections were drained (without washing) and appropriate primary antibody was applied over the sections and incubated for 45 minutes.
15. The slides were washed in phosphate buffer for 5 minutes x 2 changes.
16. The slides were covered with Super Enhancer for 30 minutes.
17. The slides were washed in phosphate buffer for 5 minutes x 2 changes.
18. The slides were covered with SS Label for 30 minutes.
19. Wash in phosphate buffer for 5 minutes x 2 changes.
20. DAB substrate was prepared by diluting 1 drop of DAB chromogen to 1ml of DAB buffer.
21. DAB substrate solution was applied on the sections for 8 minutes.
22. Wash with phosphate buffer solution for 5 minutes x 2 changes.
23. The slides are washed well in running tap water for 5 minutes.
24. The sections were counterstained with Hematoxylin stain for 2 seconds (1 dip).
25. The slides are washed in running tap water for 3 minutes.
26. The slides are air dried, cleared with xylene and mounted with DPX.

ANNEXURE V

QUICK SCORE SYSTEM- ER, PR and AR	
Score for Proportion	**Score for Intensity**
0 = no staining 1 = <1 percent nuclei staining 2 = 1-10 percent nuclei staining 3 = 11-33 percent nuclei staining 4 = 34-66 percent nuclei staining 5 = 67-100 percent nuclei staining	0 = no staining 1 = weak staining 2 = moderate staining 3 = strong staining

The scores are added together to obtain a total score that can range from 0 to 8. Tumors scoring 2 or less are negative and have a negligible chance of response.

STAINING PATTERN AND HER2 NEU SCORING

STAINING PATTERN	SCORE	HER 2/neu ASSESSMENT
No staining or membrane staining observed in <10% of tumor cells	0	Negative
A faint/barely perceptible membrane staining observed in >10% of the tumor cells	1+	Negative
A weak to moderate complete membrane staining observed in >10% of the tumor cells.	2+	Positive
A strong complete membrane staining observed in >30% of the tumor cells.	3+	Positive

ANNEXURE-VI

TNM Classification of carcinomas of the breast:

T	-	Primary Tumor
T_X	-	Primary tumor cannot be assessed
TO	-	No evidence of primary tumor
TIS	-	Carcinoma in situ
TIS (DCIS)	-	Ductal carcinoma in situ
TIS (LCIS)	-	Lobular carcinoma in situ
TIS (Paget)	-	Paget disease of the nipple with no tumor

Note : Paget disease associated with a tumor is classified according to the size of the tumor

T1	-	Tumor 2 cm or less in greatest dimension
TMIC	-	Micro invasion 0.1 cm or less in greatest dimension
T1a	-	more than 0.1 cm but not more than 0.5cm in greatest dimension
T1b	-	more than 0.5 cm but not more than 1 cm in greatest dimension.
T1c	-	more than 1 cm but not more than 2 cm in greatest dimension
T2	-	Tumour more than 2 cm but not more than 5 cm in greatest dimension.
T3	-	Tumour more than 5 cm in greatest dimension
T4	-	Tumour of any size with direct extension to chest wall or skin only as described in T4a to T4d.

Note : Chest wall includes ribs, intercostals muscles, and seratus anterior muscle but not pectoral muscle.

T4a	-	Extension to chest wall
T4b	-	Oedema (including peau'd orange) ulceration of the skin of the breast (or) satellite skin nodules confined to the same breast.
T4c	-	Both 4a and 4b, above
T4d	-	Inflammatory Carcinoma.

Notes : Microinvasion is the extension of cancer cells beyond the basement membrane into the adjacent tissues with no focus more than 0.1 cm in greatest dimension. When there are multiple foci of microvasion, the size of only the largest focus is used to classify the microinvasion.

Inflammatory carcinoma of the breast is characterized by diffuse brawny induration of the skin with an erysipeloid edge, usually with no underlying mass. If the skin biopsy is negative

and there is no localized measurable primary cancer, the T category is PTX when pathologically staging a clinical inflammatory carcinoma (T4d). Dimpling of the skin, nipple retraction, or other skin changes, except those in T4p and T4d may occur in T1, T2, or T3 without affecting the classification.

N - Regional Lymph Nodes

Nx - Regional lymph nodes cannot be assessed previously removed

N0 - No regional lumph node metastasis.

N1 - Metastasis in movable ipsilateral axillary lymph node (s)

N2 - Metastasis in fixed ipsilateral axillary lymph node (8) or in Clinically apparent ipsilateral internal mammary lymph node(s) in the absence of clinically evident axillary lymph node metastasis.

N2a - Metastasis in axillary lymph node(s) fixed to one another or to other structures.

N2b - Metastasis only in clinically apparent internal mammary lymph node (s) and in the absence of clinically evident axillary lymph node metastasis.

N3 - Metastasis in ipsilateral infraclavicular lymph node (s) with or without axillary lymph node involvement, or in clinically apparent ipsilateral internal mammary lymph node (s) in the presence of clinically evident axillary lymph node metastasis or metastasis in ipsilateral supraclavicular lymph node (s) with or without axillary or internal mammary lymph node involvement.

N3a - Metastasis in intraclavicular lymphnode(s)

N3b - Metastasis in supraclavicular lymph nodes

M - Distant metastasis

Mx - Distant metastasis cannot be assessed

M0 - No distant metastasis

M1 - Distant metastasis

MASTER CHART

S.NO	HPE NO	Age	Side	TL	SIZE	HT	G	LVI	LYI	N	SK	LN	AL	ER	PR	H2N	AR
1	24/14	50	R	CQ	6X4X3	IDC NOS	III	P	P	A	A	16/17	ADH	POS	POS	NEG	
2	328/14	63	R	UOQ	4X3X3	IDC NOS	II	P	A	A	A	3/5	FCD	POS	POS	NEG	
3	366/14	55	L	UIQ	2X2X2	IDC NOS	II	A	A	A	A	3/8	FCD	POS	POS	NEG	
4	407/14	43	R	UIQ	4X3X2	IDC NOS	I	A	P	A	A	4/5	FCD	POS	POS	POS	
5	410/14	70	R	CQ	5X2X1	IDC NOS	II	A	A	P	A	0/9	FA	NEG	NEG	NEG	
0	706/14	57	L	LOQ	6X4X2	IDC NOS	I	A	P	A	A	0/5		NEG	POS	POS	
7	724/14	37	L	CQ	1X1X1	IDC NOS	III	P	A	P	A	1/4		POS	POS	NEG	
8	1034/14	53	R	LOQ	4X2X2	IDC NOS	II	P	A	P	P	2/5	ADH	NEG	NEG	NEG	
9	1082/14	52	R	CQ	9X5X1	IDC NOS	II	P	P	A	A	2/7	FCD	POS	POS	POS	
10	1126/14	44	R	CQ	4X2X2	IDC NOS	I	A	A	P	A	3/5	FCD	POS	NEG	NEG	
11	1151/14	45	L	UOQ	6x6x3	IDC NOS	II	p	p	p	P	1/9	DCIS	POS	POS	NEG	
12	1692/14	45	L	UOQ	6X5X2	IDC NOS	I	A	P	A	A	0/7		POS	POS	NEG	0+0
13	1793/14	75	L	CQ	5X5X3	IDC NOS	II	P	P	P	A	1/2	FCD	NEG	NEG	NEG	
14	1964/14	40	R	UOQ	3X2X1	IDC NOS	II	A	A	A	A	0/3		NEG	NEG	NEG	
15	2003/14	53	L	CQ	2X1X1	IDC NOS	II	A	P	P	A	0/3		NEG	NEG	POS	
16	2177/14	55	R	UOQ	7X5X3	IDC NOS	II	A	A	A	A	2/5	FCD	POS	POS	NEG	
17	2237/14	49	R	CQ	9X5X4	IDC NOS	II	A	P	A	P	0/14	FCD	POS	NEG	NEG	
18	2355/14	37	L	UOQ	4X4X3	IDC NOS	II	A	P	A	A	19/20		NEG	NEG	POS	0+0
19	2506/14	35	L	LIQ	6X5X4	METAPLASTIC		A	P	P	A	0/9		NEG	NEG	NEG	1+4
20	2758/14	45	L	CQ	10X9X8	IDC NOS	II	A	P	A	P	3/4		NEG	POS	NEG	
21	2751/14	45	L	CQ	5X1X1	IDC NOS	I	A	P	A	A	2/3	FCD	NEG	NEG	NEG	
22	2899/14	45	R	LIQ	2X2X1	IDC NOS	I	P	A	A	A	0	FCD	POS	POS	NEG	
23	3044/14	35	L	UOQ	4X3X2	IDC NOS	II	P	A	P	A	6/13		POS	POS	NEG	
24	3072/14	33	L	CQ	4X3X2	IDC NOS	I	P	A	A	A	0/8	FCD	POS	POS	NEG	1+4
25	3188/14	45	R	CQ	6X5X4	IDC NOS	I	A	A	A	A	2/7		NEG	NEG	NEG	
26	3251/14	47	R	UOQ	3X2X2	IDC NOS	II	A	A	A	A	0/2		POS	NEG	NEG	
27	3261/14	44	R	UIQ	5X2X2	IDC NOS	I	A	A	A	A	0	FCD	POS	POS	NEG	
28	3309/14	55	L	UIQ	4X2X1	IDC NOS	II	P	P	A	A	1/2	FCD	NEG	NEG	NEG	
29	3340/14	45	R	CQ	5X4X4	IDC NOS	II	P	P	A	A	3/4	DCIS	NEG	POS	NEG	
30	3349/14	49	L	LOQ	3X3X2	IDC NOS	I	P	P	P	A	3/13	FA	NEG	NEG	NEG	
31	3462/14	45	R	CQ	5X4X4	IDC NOS	I	P	P	P	A	10/13		NEG	NEG	NEG	
32	3509/14	50	L	LOQ	3X3X3	IDC NOS	I	A	A	A	A	1/5		POS	NEG	POS	

33	3536/14	58	R	UIQ	2X2X1	LOBULAR		A	A	A	A	0/5		POS	POS	NEG	2+5
34	3648/14	47	L	UOQ	3X3X2	IDC NOS	II	P	A	A	A	1/8	FCD	POS	NEG	NEG	
35	3686/14	40	L	UOQ	4X3X3	IDC NOS	II	A	A	A	A	1/10		NEG	NEG	NEG	
36	4029/14	50	R	UIQ	3X3X2	IDC NOS	II	A	P	A	A	14/23	FCD	NEG	NEG	NEG	
37	4108/14	63	R	UOQ	2X2X1	IDC NOS	I	A	P	A	A	1/8	FA	NEG	NEG	NEG	
38	4240/14	50	L	CQ	1X1X1	IDC NOS	I	P	A	A	A	0/3	UDH	POS	POS	NEG	
39	4290/14	48	L	UIQ	7X2X3	IDC NOS	II	P	A	A	P	7/9	FCD	NEG	NEG	NEG	
40	4589/14	49	R	UOQ	2X1X1	IDC NOS	III	P	P	P	A	3/4	SA	POS	POS	POS	0+0
41	4590/14	37	L	UIQ	5X3X2	IDC NOS	I	A	A	A	A	9/10	DCIS	NEG	POS	NEG	
42	4603/14	42	R	UIQ	1X1X1	IDC NOS	II	P	P	P	A	11/12	DCIS	POS	POS	NEG	
43	4757/14	52	R	UOQ	4X3X2	IDC NOS	II	P	P	A	A	4/7	FCD	POS	POS	NEG	
44	4812/14	63	L	CQ	6X5X3	IDC NOS	II	P	P	A	A	0/1	FCD	POS	POS	NEG	
45	4814/14	46	L	CQ	5X4X2	IDC NOS	II	A	A	A	P	11/17	FCD	NEG	NEG	NEG	
46	4818/14	60	R	CQ	3X2X2	MUCINOUS		A	A	A	A	0		POS	NEG	NEG	0+0
47	5009/14	65	R	LOQ	5X4X2	NEUROENDOCRINE		P	P	A	A	1/2		POS	NEG	NEG	1+5
48	4890/14	50	L	CQ	5X2X2	PAPILLARY		A	A	A	A	0		POS	POS	NEG	0+0
49	5102/14	52	L	UIQ	9X6X4	IDC NOS	II	P	A	A	A	1/5		POS	NEG	POS	
50	5206/14	51	L	CQ	8X2X2	IDC NOS	II	A	A	A	P	4/5	FCD	NEG	NEG	NEG	
51	5277/14	45	R	CQ	4X3X2	IDC NOS	II	A	A	A	A	0/14	FCD	POS	NEG	NEG	
52	5306/14	60	R	CQ	1X1X1	IDC NOS	II	P	P	A	A	6/7	FCD	NEG	NEG	NEG	
53	5332/14	56	R	CQ	3X3X1	MUCINOUS		A	A	A	A	0/7	FCD	POS	POS	NEG	1+2
54	5353/14	50	L	CQ	3X3X1	MEDULLARY		A	P	A	A	1/5	FCD	NEG	NEG	NEG	0+0
55	5427/14	45	R	CQ	4X2X2	IDC NOS	II	A	A	A	A	1/5	FCD	POS	POS	NEG	
56	5429/14	49	R	CQ	4X3X2	IDC NOS	II	A	A	A	A	4/9	FCD	POS	POS	NEG	
57	5819/14	54	R	CQ	8X6X3	METAPLASTIC		A	P	A	A	0/10		NEG	NEG	NEG	0+0
58	6189/14	65	R	UOQ	6X4X3	MUCINOUS		P	A	A	A	1/9		POS	POS	NEG	1+5
59	6194/14	45	L	CQ	9X5X1	IDC NOS	II	P	P	A	P	1/8	FCD	POS	POS	NEG	
60	6219/14	65	L	CQ	4X3X3	IDC NOS	III	P	A	P	A	0/7	FCD	NEG	NEG	NEG	
61	6266/14	70	L	CQ	6X4X2	IDC NOS	II	A	A	A	P	0/4	FCD	POS	POS	NEG	0+0
62	6309/14	60	R	CQ	4X3X2	IDC NOS	I	A	P	A	A	14/19	UDH	POS	POS	NEG	1+2
63	6376/14	37	L	LOQ	4X3X1	IDC NOS	II	A	A	P	A	4/9	FA	NEG	NEG	NEG	
64	6655/14	50	L	CQ	3X3X1	IDC NOS	III	P	A	A	A	2/3	FCD	POS	POS	POS	0+0
65	7004/14	35	R	CQ	4X3X2	IDC NOS	II	P	P	P	A	0/7	DCIS	NEG	POS	POS	

66	7125/14	67	R	UOQ	2X1X1	IDC NOS	II	A	P	P	A	0/6	FCD	POS	POS	NEG	
67	7209/14	55	L	LOQ	1X1X1	IDC NOS	II	P	P	A	A	0/7	FCD	POS	POS	NEG	
68	7302/14	48	L	UOQ	3X2X1	IDC NOS	II	P	A	A	A	0/3		NEG	NEG	NEG	
69	7321/14	52	R	CQ	5X3X3	APOCRINE		A	P	A	A	1/4		NEG	NEG	NEG	2+5
70	7332/14	47	R	UOQ	3X3X2	IDC NOS	II	A	A	A	A	0	FCD	NEG	NEG	POS	0+0
71	7435/14	46	R	UIQ	5X4X2	IDC NOS	II	A	A	P	A	5/8	FCD	NEG	NEG	NEG	
72	7516/14	55	R	CQ	3X2X2	IDC NOS	II	A	A	A	A	1/11		POS	POS	POS	
73	7559/14	63	R	UOQ	1X1X1	APOCRINE		A	P	A	A	4/19		NEG	NEG	NEG	1+2
74	7721/14	33	R	UIQ	4X4X3	IDC NOS	II	A	P	P	A	9/10	FA	POS	POS	NEG	
75	7733/14	52	R	CQ	3X2X2	IDC NOS	II	P	P	A	A	3/8	SA	POS	POS	NEG	0+0
76	7755/14	46	R	UOQ	3X3X3	MEDULLARY		A	P	A	A	0		NEG	NEG	NEG	0+0
77	7839/14	57	L	CQ	3X2X1	IDC NOS	II	A	P	P	A	4/5		NEG	NEG	NEG	
78	8076/14	56	R	UOQ	1X1X1	IDC NOS	II	P	A	P	P	9/10	DCIS	POS	NEG	POS	
79	8280/14	60	R	CQ	2X2X2	IDC NOS	II	A	P	A	A	0/5	FCD	NEG	NEG	NEG	
80	8287/14	55	R	CQ	3X2X2	IDC NOS	II	P	A	A	A	1/4		POS	NEG	NEG	
81	8327/14	55	L	UOQ	3X2X2	IDC NOS	III	P	P	P	A	2/5	FCD	NEG	NEG	NEG	
82	8383/14	53	L	UOQ	6X4X4	IDC NOS	II	P	P	P	A	2/7		NEG	NEG	NEG	
83	8459/14	46	L	UOQ	9X8X4	IDC NOS	II	P	P	P	P	2/9	FCD	POS	POS	NEG	
84	8503/14	60	R	CQ	5X5X4	IDC NOS	III	P	P	A	A	0	DCIS	NEG	NEG	NEG	0+0
85	8572/14	40	L	UIQ	1X1X1	APOCRINE		A	A	A	P	0/17	DCIS	NEG	NEG	NEG	2+5
86	8589/14	37	R	LIQ	4X2X1	IDC NOS	III	P	P	A	A	0/4		POS	POS	NEG	
87	8672/14	50	R	CQ	3X2X2	IDC NOS	I	P	P	A	A	1/11	FA	NEG	NEG	POS	
88	8932/14	40	L	CQ	2X2X1	IDC NOS	I	P	P	A	A	1/6	FA	POS	POS	NEG	
89	9065/14	30	L	UOQ	4X3X3	IDC NOS	III	A	A	A	P	1/2	FCD	POS	POS	POS	2+4
90	9083/14	45	L	UOQ	2X1X1	IDC NOS	II	P	P	P	A	0/4		POS	POS	NEG	
91	9229/14	57	L	LOQ	2X2X1	IDC NOS	II	P	A	A	A	5/6	FCD	NEG	NEG	POS	
92	9247/14	65	L	UOQ	4X2X1	IDC NOS	I	A	P	A	A	2/3	DCIS	POS	POS	NEG	2+5
93	9275/14	60	L	CQ	8X5X4	IDC NOS	III	P	A	P	P	0	FCD	POS	POS	NEG	
94	9437/14	46	L	UIQ	3X2X2	IDC NOS	III	A	A	P	A	0/4		NEG	NEG	NEG	
95	9438/14	56	R	CQ	2X2X1	IDC NOS	II	A	A	A	A	4/5		POS	POS	NEG	
96	9444/14	30	R	CQ	3X2X2	METAPLASTIC		A	A	A	A	0/5		NEG	NEG	NEG	0+0
97	9667/14	40	L	CQ	5X4X2	IDC NOS	II	A	P	P	A	1/3	FCD	POS	POS	NEG	
98	9762/14	44	R	LOQ	4X3X2	IDC NOS	II	P	P	P	A	0/2	FA	POS	POS	POS	

99	9956/14	40	L	UIQ	6X4X4	IDC NOS	I	A	P	A	A	0/5	FA	POS	POS	NEG	
100	10005/14	52	L	CQ	3X2X2	IDC NOS	II	A	P	A	A	1/12	FCD	NEG	NEG	POS	
101	10119/14	31	R	UOQ	6X4X4	IDC NOS	II	A	A	A	A	0/16	FCD	POS	POS	NEG	
102	10371/14	40	R	CQ	3X2X1	IDC NOS	II	P	P	A	A	7/11	ADH	POS	POS	NEG	
103	10407/14	43	R	CQ	4X3X3	IDC NOS	I	P	A	A	A	2/19	FCD	NEG	NEG	POS	1+3
104	10449/14	45	L	CQ	6X4X4	IDC NOS	III	A	A	A	A	1/13	FCD	NEG	NEG	NEG	0+0
105	10469/14	45	R	CQ	2X1X1	IDC NOS	II	P	A	P	A	3/5	FA	POS	POS	NEG	
106	10540/14	53	L	UOQ	2X2X1	IDC NOS	II	P	A	P	A	4/5	FCD	POS	POS	POS	3+5
107	10598/14	67	L	CQ	3X3X2	IDC NOS	II	P	A	A	A	0/7	FCD	POS	NEG	POS	
108	10850/14	55	R	CQ	7X6X2	IDC NOS	II	P	A	A	A	1/4	FA	NEG	NEG	POS	
109	10939/14	50	R	CQ	6X4X3	IDC NOS	III	P	P	A	A	16/17	ADH	POS	POS	NEG	0+0
110	11008/14	63	R	UOQ	4X3X3	IDC NOS	II	P	A	A	A	3/5	FCD	POS	POS	NEG	1+2
111	11141/14	50	R	UOQ	7X6X6	IDC NOS	II	A	P	P	P	0/8	FCD	POS	POS	POS	
112	11184/14	67	L	CQ	4X3X3	IDC NOS	III	A	P	A	A	0/8	FCD	NEG	NEG	NEG	
113	11314/14	45	L	CQ	2X2X2	IDC NOS	II	A	A	P	A	0/8	FCD	NEG	POS	POS	
114	11413/14	50	R	CQ	3X3X2	IDC NOS	II	A	P	P	A	0		NEG	NEG	POS	
115	11474/14	50	L	UOQ	3X2X2	IDC NOS	II	P	P	P	A	0/12	FCD	NEG	NEG	NEG	
116	11537/14	65	L	UOQ	3X3X3	IDC NOS	III	A	A	A	A	0/12	FCD	POS	POS	NEG	2+5
117	11719/14	42	L	UOQ	3X2X2	IDC NOS	I	P	P	P	A	1/10	FCD	NEG	NEG	POS	
118	11889/14	37	R	UOQ	3X2X1	IDC NOS	II	A	A	A	A	2/5	FCD	POS	NEG	NEG	
119	11928/14	60	R	CQ	6X2X2	IDC NOS	II	P	P	P	A	0/2		NEG	NEG	POS	
120	11994/14	42	R	CQ	6X3X3	IDC NOS	II	A	P	A	A	3/7		NEG	NEG	POS	
121	46/15	57	L	CQ	5X4X4	IDC NOS	I	A	A	A	A	0/7	FCD	NEG	NEG	POS	0+0
122	122/15	45	L	CQ	6X4X4	IDC NOS	II	A	A	P	A	0/6	FCD	NEG	NEG	POS	
123	339/15	40	R	LOQ	3X2X2	IDC NOS	II	A	A	A	A	0/5	FCD	NEG	NEG	NEG	0+0
124	352/15	46	R	CQ	3X2X2	IDC NOS	II	P	A	A	A	0/4	FCD	NEG	NEG	POS	
125	412/15	55	L	LIQ	3X3X2	IDC NOS	III	P	P	A	A	1/10	FCD	NEG	NEG	POS	
126	617/15	45	R	CQ	6X3X3	IDC NOS	I	A	P	P	A	6/7		NEG	NEG	POS	
127	703/15	55	L	CQ	2X2X1	IDC NOS	II	P	A	P	A	0		POS	POS	NEG	3+5
128	1097/15	40	R	CQ	8X8X6	IDC NOS	III	P	A	A	P	0/12	ADH	NEG	NEG	POS	2+4
129	1157/15	50	R	LIQ	6X5X4	IDC NOS	II	A	A	A	A	0/11	FCD	NEG	NEG	NEG	
130	1240/15	55	R	UIQ	2X2X2	IDC NOS	I	A	P	A	A	0/10		NEG	NEG	NEG	0+0
131	1198/15	30	L	LOQ	4X3X2	IDC NOS	I	A	P	A	A	5/8	FCD	POS	POS	NEG	

132	1334/15	37	R	CQ	3X3X2	IDC NOS	II	A	A	A	A	0/6	FCD	POS	POS	NEG	
133	1424/15	50	R	UOQ	5X3X1	IDC NOS	I	A	A	A	A	4/9	DCIS	POS	POS	POS	3+5
134	1586/15	60	L	UOQ	12X9X8	METAPLASTIC		A	A	P	A	0/22	FCD	NEG	NEG	NEG	
135	1590/15	60	R	CQ	5X3X2	IDC NOS	II	A	P	A	A	0/7	FCD	NEG	NEG	POS	1+4
136	1600/15	35	L	UIQ	8X4X3	IDC NOS	II	P	P	P	P	13/16	FCD	POS	POS	POS	
137	1689/15	50	L	UOQ	5X4X3	IDC NOS	II	P	A	A	A	0/3	FCD	POS	NEG	NEG	
138	1968/15	55	R	CQ	6X4X2	IDC NOS	III	A	P	P	A	0/3	DCIS	NEG	NEG	NEG	0+0
139	2044/15	45	R	LOQ	2X2X2	IDC NOS	II	A	P	P	A	4/7	FCD	NEG	NEG	POS	1+4
140	2327/15	33	R	LOQ	3X2X1	IDC NOS	I	P	P	A	A	0	DCIS	POS	POS	POS	
141	2741/15	48	R	CQ	5X4X2	IDC NOS	I	A	A	P	A	0/16	FCD	NEG	NEG	POS	1+4
142	2840/15	43	L	CQ	4X3X3	IDC NOS	II	P	A	P	A	1/2	DCIS	POS	POS	NEG	
143	2849/15	46	R	LOQ	3X2X2	IDC NOS	I	A	A	P	A	0/3	FCD	POS	POS	NEG	
144	2858/15	55	L	LIQ	3X2X2	IDC NOS	II	A	P	A	A	3/10	DCIS	NEG	NEG	NEG	
145	2863/15	50	L	UOQ	2X2X1	IDC NOS	III	P	P	P	A	1/4	FCD	NEG	NEG	NEG	0+0
146	2995/15	40	L	UIQ	5X3X2	IDC NOS	II	A	P	P	A	0/6		NEG	NEG	POS	
147	3115/15	54	R	UOQ	2X2X1	IDC NOS	II	A	P	P	A	0/10	FCD	NEG	NEG	NEG	
148	152/13	43	L	UIQ	5X4X2	IDC NOS	III	P	P	A	A	5/11	SA	NEG	NEG	NEG	
149	158/13	37	L	UIQ	6X2X1	IDC NOS	III	P	P	A	A	6/7		POS	POS	NEG	
150	270/13	48	L	UIQ	2X2X1	IDC NOS	III	P	P	P	A	6/7	FA	NEG	NEG	POS	
151	336/13	65	R	UOQ	3X2X2	IDC NOS	II	A	A	A	A	3/10		NEG	NEG	NEG	
152	575/13	55	R	CQ	4X3X3	IDC NOS	II	A	A	A	A	0/9	FCD	NEG	NEG	NEG	
153	1012/13	52	L	LOQ	18X16X9	IDC NOS	II	P	P	A	A	1/10	FCD	NEG	NEG	NEG	
154	1069/13	62	R	UOQ	4X4X3	IDC NOS	I	P	P	A	A	11/13		POS	NEG	NEG	
155	1081/13	43	R	CQ	4X2X2	IDC NOS	II	P	P	A	A	1/4	FCD	POS	POS	NEG	
156	1434/13	54	R	UOQ	3X2X2	IDC NOS	III	P	P	A	A	1/11	SA	POS	POS	NEG	
157	1472/13	43	L	CQ	5X4X3	IDC NOS	II	P	P	P	A	2/3	DCIS	NEG	NEG	NEG	
158	1721/13	38	L	UOQ	5X3X3	IDC NOS	III	A	P	A	A	1/8	FA	NEG	NEG	NEG	
159	1873/13	60	L	LIQ	6X5X4	IDC NOS	III	A	P	A	A	0/11	DCIS	NEG	NEG	NEG	
160	1899/13	50	L	CQ	3X2X2	IDC NOS	III	A	A	A	A	4/7	FCD	NEG	NEG	NEG	
161	2351/13	35	L	UOQ	4X3X3	IDC NOS	III	P	P	P	A	4/9	SA	NEG	NEG	NEG	
162	2775/13	45	R	CQ	5X5X1	IDC NOS	II	P	A	P	A	0/13		NEG	NEG	POS	
163	2959/13	65	L	CQ	5X3X1	IDC NOS	II	A	A	A	A	1/4	FCD	POS	POS	NEG	
164	2984/13	46	L	UOQ	3X3X3	IDC NOS	II	A	P	A	A	1/10	FCD	NEG	NEG	NEG	

165	3074/13	31	R	LIQ	3X2X1	IDC NOS	II	A	A	P	A	1/2		POS	POS	POS	
166	3176/13	55	R	UIQ	5X3X3	IDC NOS	II	P	P	P	A	3/5		POS	POS	NEG	
167	3240/13	46	L	LOQ	4X4X4	IDC NOS	II	P	A	A	A	0/8		NEG	NEG	NEG	
168	3249/13	60	L	CQ	7X6X2	IDC NOS	II	A	P	P	A	3/7	FCD	NEG	NEG	POS	
169	3379/13	37	R	UOQ	2X2X2	IDC NOS	II	P	P	P	A	0/6	FCD	POS	POS	NEG	
170	3428/13	43	R	UOQ	4X3X3	IDC NOS	I	A	P	A	A	4/5	FCD	POS	POS	NEG	
171	3446/13	55	R	CQ	3X3X2	IDC NOS	III	P	P	A	A	1/10	SA	POS	POS	POS	
172	3496/13	55	L	UIQ	8X8X6	IDC NOS	II	A	A	A	A	0/12		NEG	NEG	POS	
173	3501/13	54	R	UOQ	4X4X3	IDC NOS	II	P	P	A	A	0/3		NEG	NEG	NEG	
174	3928/13	43	R	CQ	3X2X2	IDC NOS	II	P	P	A	A	2/5	FA	NEG	NEG	POS	
175	4161/13	48	L	LOQ	4X3X3	IDC NOS	I	A	P	A	A	7/8	FA	POS	POS	NEG	
176	4478/13	33	L	UOQ	7X6X5	IDC NOS	III	P	A	A	A	1/4	FCD	POS	POS	NEG	
177	4753/13	60	L	UIQ	6X4X2	IDC NOS	III	A	A	P	A	0/6		POS	POS	POS	
178	4918/13	35	R	CQ	8X4X3	IDC NOS	II	P	P	A	A	0/3	DCIS	NEG	NEG	POS	
179	5429/13	62	L	UIQ	3X3X2	IDC NOS	II	A	P	A	A	6/7		POS	POS	NEG	
180	5457/13	45	R	UOQ	4X4X3	MUCINOUS		P	A	A	A	3/4		POS	POS	NEG	0+0
181	5882/13	60	L	CQ	2X2X1	LOBULAR		A	P	A	A	0		POS	POS	NEG	1+3
182	6359/13	55	R	CQ	5X4X3	METAPLASTIC		P	A	A	A	0/5		NEG	NEG	NEG	3+4
183	6884/13	50	R	CQ	8X6X5	METAPLASTIC		P	A	A	A	0/8		NEG	NEG	NEG	0+0
184	7093/13	75	R	UOQ	4X4X3	MUCINOUS		P	A	A	A	3/11	FCD	POS	POS	NEG	1+3
185	7153/13	42	R	UOQ	6X5X3	IDC NOS	I	P	P	A	A	1/6	DCIS	POS	POS	NEG	
186	7160/13	35	L	UOQ	6X4X3	IDC NOS	III	P	P	P	A	5/11	FCD	NEG	NEG	NEG	
187	7173/13	60	L	UOQ	6X5X4	IDC NOS	I	A	A	A	A	0/6	FCD	POS	POS	NEG	0+0
188	7478/13	67	L	UIQ	7X7X2	APOCRINE		A	A	A	A	0/5	FCD	NEG	NEG	NEG	
189	7750/13	42	L	CQ	5X3X1	IDC NOS	II	A	P	A	A	3/7	FA	NEG	NEG	NEG	
190	8322/13	65	R	UIQ	3X2X2	IDC NOS	II	P	P	P	A	5/8	FCD	POS	POS	NEG	
191	8329/13	59	R	CQ	5X4X3	LOBULAR		A	P	A	A	0/2	DCIS	POS	POS	NEG	2+5
192	8593/13	45	R	CQ	2X2X2	IDC NOS	III	A	A	A	A	4/7	FCD	NEG	NEG	NEG	
193	8776/13	47	L	CQ	4X3X2	IDC NOS	II	A	P	P	A	1/8	FCD	NEG	NEG	POS	
194	9073/13	67	R	CQ	8X4X3	IDC NOS	II	A	A	P	A	0	FCD	POS	POS	NEG	
195	9156/13	40	R	LOQ	3X2X2	IDC NOS	I	P	A	A	A	1/4	FCD	POS	POS	NEG	
196	9914/13	45	R	CQ	3X3X3	IDC NOS	II	P	P	P	A	0/3	DCIS	POS	POS	POS	
197	10042/13	59	L	LIQ	4X4X4	IDC NOS	II	P	A	A	A	1/11		POS	NEG	POS	

198	10144/13	47	L	CQ	5X2X1	IDC NOS	III	A	A	A	A	4/5		POS	POS	NEG	
199	10417/13	38	R	CQ	8X8X6	IDC NOS	II	A	A	A	A	0	FA	POS	POS	NEG	
200	10473/13	43	L	CQ	6X5X4	IDC NOS	II	P	P	A	A	2/3		POS	POS	POS	
201	10502/13	67	R	LIQ	4X3X3	IDC NOS	II	A	A	P	A	6/11	FCD	NEG	NEG	NEG	
202	10658/13	35	R	UIQ	2X1X1	IDC NOS	II	P	P	A	A	2/3	FCD	NEG	NEG	POS	
203	10667/13	59	R	LOQ	3X2X2	IDC NOS	II	A	A	P	A	9/10		POS	POS	NEG	
204	10680/13	75	R	CQ	1X1X1	IDC NOS	I	A	P	A	A	5/7	ADH	POS	POS	POS	
205	10885/13	53	L	UOQ	2X2X1	IDC NOS	II	A	P	P	A	8/9	FCD	POS	POS	NEG	
206	10898/13	54	L	UOQ	6X4X4	IDC NOS	II	P	P	A	A	1/3	FCD	NEG	NEG	NEG	
207	11034/13	49	R	CQ	5X4X3	IDC NOS	II	A	A	A	A	3/7	FA	POS	POS	NEG	
208	11124/13	50	R	UIQ	3X2X1	IDC NOS	II	P	P	A	A	4/7	SA	POS	POS	NEG	
209	11136/13	35	R	UOQ	9X5X1	IDC NOS	III	A	A	P	A	2/3		POS	POS	NEG	
210	11142/13	52	L	CQ	4X3X1	IDC NOS	II	P	P	A	A	5/9	FCD	POS	POS	POS	
211	11234/13	51	L	LOQ	2X2X2	IDC NOS	I	P	P	A	A	0/6		NEG	NEG	NEG	
212	11294/13	47	R	CQ	5X3X3	IDC NOS	II	A	P	P	A	1/2	FCD	NEG	NEG	NEG	

KEY TO MASTER CHART

R	:	Right
L	:	Left
TL	:	Tumor Location
UOQ	:	Upper Outer Quadrant
UIQ	:	Upper Inner Quadrant
CQ	:	Central Quadrant
LIQ	:	Lower Inner Quadrant
LOQ	:	Lower Outer Quadrant
HT	:	Histological Type
IDC NOS	:	Infiltrating Ductal Carcinoma- Not Otherwise Specified
PAPILLARY	:	Papillary Carcinoma
MEDULLARY	:	Medullary Carcinoma
METAPLASTIC	:	Metaplastic Carcinoma
MUCINOUS	:	Mucinous Carcinoma
APOCRINE	:	Apocrine Carcinoma
LOBULAR	:	Lobular Carcinoma
G	:	Grade
AL	:	Associated Lesion
DCIS	:	Ductal Carcinoma InSitu

FCD	:	Fibrocystic Disease
SA	:	Selerosing Adenosis
UDH	:	Usual Ductal Hyperplasia
ADH	:	Atypical Ductal Hyperplasia
LVI	:	LymphoVascular Invasion
LYI	:	Lymphocytic Infiltration
N	:	Necrosis
SK	:	Skin Involvement
LN	:	Lymph Node Status
ER	:	Estrogen Receptor
PR	:	Progestrone Receptor
AR	:	Androgen Receptor
H2N	:	HER2neu
A	:	Absent
P	:	Present
POS	:	Positive
NOS	:	Negative